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Brain activity of upper limb movement in healthy and pathological aging: perspectives for post-stroke rehabilitation

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Camille Muller. Brain activity of upper limb movement in healthy and pathological aging: perspectives for post-stroke rehabilitation. *Neurons and Cognition [q-bio.NC]*. Université de Montpellier, 2023. English. NNT: 2023UMONS029 . tel-04892259

HAL Id: tel-04892259

<https://theses.hal.science/tel-04892259v1>

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THÈSE POUR OBTENIR LE GRADE DE DOCTEUR DE L'UNIVERSITÉ DE MONTPELLIER

En Sciences du Mouvement Humain

École doctorale Sciences du Mouvement Humain (ED463)

Unité de recherche EuroMov Digital Health in Motion

Effets du vieillissement sain et pathologique sur l'activité cérébrale lors du mouvement du membre supérieur : *perspectives pour la rééducation post-AVC*

Brain activity of upper limb movement in healthy and pathological aging:
perspectives for post-stroke rehabilitation

Présentée par **Camille MULLER**

Le 3 avril 2023

Sous la direction d'Isabelle LAFFONT (directrice),
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DE MONTPELLIER

Remerciements

Il est difficile de trouver les bons mots pour remercier toutes les personnes qui m'ont accompagnée et aidée tout au long de cette éprouvante aventure ; les scientifiques avec qui j'ai échangé tout au long de ce travail, ceux qui m'ont encadrée, les ami-e-s, la famille, et toutes ces personnes qui ont eu à un moment un impact sur l'aboutissement de ce travail. Ceux qui me connaissent le savent, dire les choses de manière concise n'est pas une de mes qualités, d'autant plus que pendant toutes ces années, j'ai eu la chance d'être extrêmement bien entourée et je veux personnellement remercier toutes ces personnes.

Je remercie le Pr. **Isabelle Bonan** et le Pr. **Cédric Albinet**, d'avoir accepté de rapporter ce travail et pour leurs précieux retours. Je remercie aussi le Dr. **Laurence Paire-Ficout** et le Pr. **Thierry Lejeune**, d'avoir accepté de participer à mon jury. Je suis honorée d'avoir pu discuter de mon travail avec vous, merci pour votre temps et vos retours.

Je souhaite maintenant remercier les personnes qui m'ont encadrée, et accompagnée jusqu'à la fin, les 3 piliers de ce travail. **Isabelle**, merci pour ton soutien sans faille, pour ta bienveillance, pour toute l'aide apportée tout au long de ce travail, et pour tout ce que tu m'as transmis. **Stéphane**, merci de m'avoir fait confiance dès le début, de m'avoir accompagnée dans les moments de doutes les plus difficiles afin que je n'abandonne pas et de m'avoir tant appris. **Karima**, merci de m'avoir accueillie dans la grande famille ReArm, ça a été un véritable plaisir d'apprendre au côté d'une personne aussi travailleuse que toi, merci d'avoir été autant présente pour moi. Il est difficile de témoigner de toute ma reconnaissance pour vous 3 en quelques lignes, j'ai grandi et tellement appris à vos côtés. J'espère que nous aurons l'occasion de continuer à travailler sur des projets communs et à échanger, ça a été une énorme chance de réaliser cette thèse à vos côtés !

La direction de thèse c'est une chose, mais à EuroMov on n'est jamais bien seuls. A ceux qui m'ont accompagnée pendant tout ce travail et qui se sont investis à 1000% pour m'aider, merci ! **Denis**, merci d'avoir su m'écouter et m'aider pendant les moments de doutes, tu as été un véritable pilier pour moi. **Makii**, many thanks for everything you've taught me. Thank you for the time you gave me, and for your patience with me. I've learned so much from you. **Gérard**, travailler avec toi a été un véritable plaisir, je te remercie infiniment pour toute la confiance que tu m'as accordée. **Binbin**, merci pour ta patience, ton temps et ton aide.

Au cours de ce travail j'ai jonglé entre deux mondes, le laboratoire et l'hôpital. Alors je tiens à remercier tout particulièrement les personnes qui m'ont si bien accueillie et aidée, et qui sont responsables du bon déroulement de ce projet. Du côté du **CHU de Lapeyronie**, je remercie **Christelle Giraudie**, **Thomas Goiz**, **Claire**, **Valérie**, et tous ceux qui ont participé de près ou de loin à rendre mon passage si instructif. Du côté du **CHU du Grau du Roi**, je remercie chaleureusement **Marion et Jérôme** pour leur accueil et leur confiance. De manière plus globale, j'adresse un immense remerciement à tous les participants des études et à toutes les personnes impliquées dans le beau **projet ReArm** de Karima ; stagiaires, doctorants, post-doc, kinés, ergos, médecins, Du côté du laboratoire, pour leur aide précieuse, je remercie **Simon et Pierre**, sans qui ce travail n'aurait pu aboutir.

Aux personnes qui ont formé mon comité de suivi de thèse, et qui m'ont accompagnée pendant ces 4 années, merci ! **Jacky**, merci pour ta bonne humeur, ton soutien et ton accueil au labo ! **Julie**, merci d'avoir toujours été présente quand j'en avais besoin, tu as su m'aider à ne pas m'égarer au milieu de mes crises d'angoisses, et je t'en suis très reconnaissante ! **Wei-Peng**, so many thanks for taking part of my thesis steering committee. Having a chance to exchange on my work with you was a real honor, I hope we will have a chance to work on a joint project one day!

Vivre une thèse à EuroMov c'est, à mon sens, vivre une thèse dans les meilleures conditions possibles. C'est découvrir des personnes avec lesquelles on partage certes le goût de la science, du sport mais aussi des personnes toujours là pour aider, pour rigoler, pour sortir un peu la tête de l'eau. Que ce soit au travers d'échanges scientifiques, de questions, ou pour des discussions plus légères, **Alain**, **Pierrick**, **Julien**, **Yannick**, **Grégoire**, **Pierre B**, **Loïc**, **Pierre S**, **Sébastien**, **Nico**, **Benoit**, **Gilles**, ... merci !

Que ce soit pour partager un bureau, pour les pauses café, pour imaginer des projets sans fins, ou pour discuter de la prochaine sortie, merci aux doctorants et anciens du labo avec qui j'ai eu la chance de partager cette aventure, **Ludo** (pour tes remarquables conseils), **Samar, Mélo, Clem** (pour votre soutien depuis le début), **Andrii, Alice, Gaby, Zaineb, Coralie, Alex, Zakaria, Sem, Momo, Frank, Rayane, Quentin, Grégoire ...** merci pour tout ! **Germain**, travailler avec toi a été génial, partager des projets communs m'a permis d'avancer, tu as su m'aider et m'écouter, autant que possible. Je te suis infiniment reconnaissante de tout ce que tu as apporté à ce travail. Je n'aurais pas pu imaginer meilleur binôme pour faire cette thèse ! **Vincent**, merci pour ton soutien jusqu'au bout, pour avoir été là pour me faire réviser à la dernière minute et avoir su comment me changer les idées, tu es un ami précieux !

Et au milieu de cette marée de doctorants, un petit groupe, un groupe unique, « les gars sûrs ». La seule chose dont je suis sûre avec eux, c'est que c'est une famille pour la vie, ensemble on a traversé la thèse, on a fait du théâtre, on est partis à l'aventure, et je n'ai absolument aucun doute sur la suite, où qu'on aille, quoi que l'on fasse, on sera toujours là les uns pour les autres. **MERCI, Marion**, d'avoir été là pour m'aider à toute heure et pour toute l'énergie que tu m'as transmise, tu as été un vrai pilier pour moi; **Juju**, d'avoir su comment me changer les idées dans les moments difficiles, pour toute ta bienveillance et ton amitié si précieuse; **Pauline**, pour tout ce que tu m'as apportée, tu as été un vrai modèle, et une amie vraiment géniale; **Elé**, de m'avoir soutenue et d'avoir été là même à des milliers de km, ta bonne humeur contagieuse me manque énormément mais je sais qu'on se retrouvera vite; **Louis**, pour tous tes conseils, pour ton humour douteux, et surtout pour m'avoir poussée tout du long; **Malo**, pour ton soutien, que ce soit autour d'une session EEG ou d'un cours de gym, merci pour toutes ces discussions; **Christophe**, de m'avoir changé les idées avec tes potins sans fin, et pour ta bonne humeur elle aussi sans fin; **Mathis**, d'avoir été là depuis que tu m'as servi de cobaye puis jusqu'au bout ! Merci pour tout, cette superbe aventure est en grande partie due aux personnes que j'ai rencontrées, et je me sens extrêmement chanceuse d'avoir découvert des amis aussi incroyables que vous.

Finir une thèse dans une nouvelle ville, avec une charge d'enseignement aussi conséquente n'a pas toujours été facile, mais je n'aurais pas pu mieux tomber, je remercie donc le laboratoire **ISM** et les responsables de la **FSS** de l'université Aix-Marseille, pour leur confiance et leur accueil ! Merci tout particulièrement à l'équipe **DynamiCC** pour son accueil, ceux qui m'ont accompagnée, **Lionel, Fabrice N, Fabrice S, Hadrien, Nicolas, Gilles, Christophe, Jean-Jacques, Pascale, Virginie, Nadine, Cécile, Jérôme, Sophie & Julien à Gap, Stéphanie & Cyril à Aubagne, ...** et les doctorants et anciens qui m'ont tant aidée, **Najib, Laura, Marta, Gaëtan, Dorian, Loïc, Théo, Gwen, ...** Dans cette même lignée Marseillaise, merci **Claire & Philippe** de m'avoir hébergée, vous êtes des personnes si bienveillantes et généreuses, merci pour tout !

Avant Marseille et Montpellier, il y a eu Lyon. J'ai découvert la passion de la recherche en sciences du mouvement au **LIBM**. Je remercie particulièrement, **Arnaud**, pour ce que tu m'as transmis et appris, et pour ta confiance. Ça a été un plaisir de découvrir la recherche à tes côtés ! **Angèle**, merci à toi pour ton aide sur la finalisation de nos projets communs et ton soutien ! La recherche m'aura permis de rencontrer des personnes fabuleuses, **Mathilde**, tu es une amie incroyable, merci d'avoir autant cru en moi, de m'avoir autant poussée et soutenue, d'avoir pleuré et ri avec moi, et d'être toujours là.

Cette aventure a été pavée de rencontres, et je ne peux pas faire ces remerciements sans citer la merveilleuse équipe du labo **HAVAE**, les Limougeauds et leur éternelle bienveillance. **Stéphane, Anaïck, Stéphanie, Axelle, et toute l'équipe**, vous m'avez ouvert grand les bras de la belle famille **HAVAE**, merci pour votre soutien et j'espère que nos routes se recroiseront vite !

Quittons maintenant les collègues et amis rencontrés grâce à la recherche, il est temps de prendre quelques lignes pour remercier les ami-e-s, là pour certain-e-s depuis toujours. Aux copains rencontrés à la fac, ça y est, j'arrête enfin les études ! Merci pour tout, **Louis, Galo, Maëlle, Jojo, Carla**, merci d'avoir été là jusqu'au bout malgré les différentes routes empruntées. **Léa**, merci d'avoir été là, d'avoir écouté ma répétition au concours et d'être venue voir le résultat à la fin, on en a fait du chemin depuis la L1 Gym, tu es une amie si importante, et une personne géniale. Aux copines rencontrées à la fac à Lyon, et qui êtes encore là, merci, **Juliette**, de m'avoir si bien comprise et d'avoir été là, **Pauline**, tu es une amie fantastique, merci pour ton soutien sans faille, où que la suite me mène, je sais que tu seras toujours là.

L'autre grande histoire de ma vie c'est la gym, et c'est aussi ce qui m'a permis de sortir la tête de l'eau, pour m'avoir donné la possibilité de m'entraîner, d'entraîner et de me sentir chez moi, merci à **GSL, aux gymnastes avec qui je me suis entraînée ou que j'ai entraîné**, et plus particulièrement à **Clémentine, Emilie, et Gaël**, votre soutien a été précieux. Merci aux copines rencontrées à la gym et devenues de véritables amies, **Kaury**, pour ta bienveillance et ton soutien, **Fiona, Loulou, Jeannot**, pour avoir été là malgré la distance et m'avoir soutenue.

Enfin, il y a les copains de toujours. **Louis, Guy, Neil S, Neil L, Pauline, Aliénor, Camille, Raphaël, Amélie, Clara, Roxane, Emma, Flavian, Victoria, Laurène, Arnaud, Mathilde, Magalie, Gaël, Oriane, Raph, Jullien, Max, Dylan**, mille merci pour votre amitié et votre soutien ! **MERCI, Baptiste**, d'avoir été un ami si précieux, que ce soit pour m'écouter raconter ma thèse ou pour me sortir la tête de l'eau, **Félix**, de m'avoir autant soutenue et d'être toujours là, **Antoine**, de m'avoir poussée et encouragée, tu as été un vrai pilier pour moi, **Clémence**, d'avoir été si patiente avec moi, d'être une amie si fabuleuse, si bienveillante et généreuse, tu es là depuis le début, et ça continuera longtemps. **Anne-lise**, pendant cette thèse tu as été mon repère, la personne qui m'a sortie la tête de l'eau, m'a fait tellement rire, j'ai redécouvert une amie pour la vie, merci pour tout ce que tu m'as apporté et m'apportes au quotidien. J'en profite pour remercier ta famille, **Kiki, Elisabeth & Patrice**, vous avez été une merveilleuse famille d'accueil, merci pour tout votre soutien ! **Céline, Domi, Véro, et tous les copains de mes parents** qui m'ont toujours soutenue, merci ! Enfin, **Jessy**, merci de m'avoir mentorée et accompagnée, ton soutien a été précieux !

A ceux qui sont là depuis toujours, qui m'ont toujours épaulée, soutenue, à ma famille, merci pour tout ce que vous m'avez apporté pour aller au bout de cette thèse. **MERCI**, aux oncles et tantes, **Cathy, Isa, Patrick, Cécile, Sylvie, Jean-Pierre, Stéphane**; à la famille un peu éloignée, **Madelaine, Pascale, Gérard, Sophie, Jérémie, Jacky, Paulette, et tous les autres**; aux cousins, **Julie, Marin, Coline, Clément, Jules, Jeanne V, Romain, Vincent, Jeanne A, Antoine** merci de me comprendre si bien, **Juliette & Louise** merci pour tout ce que vous m'apportez au quotidien et pour votre soutien sans faille; les grands-parents, **Mamie Charlotte & Papy Pierre**, les meilleurs cobayes, je vous suis tellement reconnaissante que vous ayez été là, et pour avoir toujours cru en moi, **Mamie Denise**, tu es une personne si forte, merci pour tout; mon petit frère, **Théo**, merci pour tout ton soutien, et pour avoir toujours cru en moi, tu es une personne tellement importante pour moi; **Alexi, Bastien, Marie-Pierre et Hervé**, merci pour votre soutien cette dernière année !

Je veux profiter de ces quelques lignes pour remercier **Papy Alain**, qui me manque tant, j'aurais tellement souhaité que tu sois encore là pour assister à la fin de ce travail sur lequel tu me posais tant de questions, tu as été un véritable modèle de curiosité et de passion, merci d'avoir toujours cru en moi, je suis convaincue que tu aurais été très fier de moi.

Enfin, je remercie ceux sans qui je ne serai pas là, mes parents, vous avez vous-aussi votre part de responsabilité dans l'aboutissement de ce travail, **papa**, toi qui as relu mes premiers jets en anglais, et qui a tant essayé de comprendre le fond du sujet pour m'aider, **maman**, toi qui as su me pousser au bout de ce weekend de l'enfer pour finaliser le manuscrit, qui a relu mon travail, l'a corrigé, m'a calmée, je n'aurais pas pu imaginer meilleurs co-pilotes pour traverser cette épreuve. Merci de m'avoir transmis la passion de la recherche, la curiosité, la détermination et l'engagement, vous n'avez jamais cessé de me pousser à être meilleure et avez cru en moi quand je n'y croyais plus, merci pour tout, je vous suis éternellement reconnaissante pour tout ce que vous faites pour moi au quotidien.

Pour finir, et bien finir, je remercie celui qui partage ma vie et sans qui cette thèse aurait été tellement plus compliquée. **Matthieu**, de loin la plus belle chose que m'aura apporté cette aventure. Merci pour tout ce que tu m'apportes au quotidien, je te dois énormément dans l'aboutissement de ce travail. Merci infiniment pour ton soutien sans faille, pour avoir su gérer mes crises d'angoisse, pour m'avoir donné confiance en moi, et m'avoir rendue meilleure et plus forte. Je n'aurais jamais de mots assez forts pour t'exprimer à quel point je te suis reconnaissante, et tout ce que tu représentes pour moi. Je me sens extrêmement chanceuse à tes côtés. Tu m'as accompagnée jusqu'au bout, et je suis absolument convaincue qu'on continuera encore à être là l'un pour l'autre pour la suite !

MERCI A TOUTES ET TOUS !!!

Scientific production arising from this thesis

Publications (original article, abstract) and Book chapters

1. **Muller, C. O.**, Muthalib, M., Mottet, D., Perrey, S., Dray, G., Delorme, M., Duflos, C., Froger, J., Xu, B., Faity, G., Pla, S., Jean, P., Laffont, I., & Bakhti, K.K. A. (2021). Recovering arm function in chronic stroke patients using combined anodal HD-tDCS and virtual reality therapy (ReArm): A study protocol for a randomized controlled trial. *Trials*, 22(1), 747. <https://doi.org/10.1186/s13063-021-05689-5>
2. **Muller, C. O.**, Perrey, S., Bakhti, K., Muthalib, M., Dray, G., Xu, B., Mottet, D., & Laffont, I. (2023). Aging effects on electrical and hemodynamic responses in the sensorimotor network during unilateral proximal upper limb functional tasks. *Behavioural Brain Research*, 443, 114322. <https://doi.org/10.1016/j.bbr.2023.114322>
3. **Muller C.O.**, Faity G., Muthalib M., Perrey S., Dray G., Xu B., Froger J., Laffont I., Delorme M., Bakhti K. (*In preparation*) Brain-movement relationship in upper-limb functional tasks for chronic post-stroke patients.

Conference presentations

Oral communications

1. **Muller C.O.**, Bakhti K.K.A., Muthalib M., Mottet D., Froger J., Delorme M., Perrey S., Laffont I. (Dec. 2022) Cortical activation of unilateral upper limb tasks: perspectives for stroke rehabilitation. *37^{ème} congrès de la société française de médecine physique et de réadaptation (SOFMER)*
2. Laffont I., Bakhti K.K.A., van Dokkum L., Muthalib M., **Muller C.O.**, Delorme M., Froger J., Jourdan C., Le Bars E., Menjot de Champfleury N., Dray G., Xu B., Perrey S., Mottet D. (Dec. 2022) From basic science to rehabilitation: knowledge in motor learning and brain activation can help to build the future of our clinical practices. *37^{ème} congrès de la SOFMER*
3. **Muller C.O.** (Sept. 2022), Quel est l'apport de l'évaluation de l'activité cérébrale liée au mouvement fonctionnel pour la rééducation post-AVC ? *Séminaire du Laboratoire HAVAE, IFLOMER, Université de Limoges*
4. **Muller C.O.**, Bakhti K.K.A., Muthalib M., Mottet D., Froger J., Delorme M., Perrey S., Laffont I. (Juil. 2022) Cortical activation of unilateral upper limb tasks: perspectives for stroke rehabilitation. *Congrès international de la société de médecine physique et de réadaptation (ISPRM)*
5. **Muller C.O.** (Juin 2022) Cerveau-mouvement : perspectives pour la rééducation post-AVC. Ma thèse en 3 minutes. *Journée de l'école doctorale SMH.*
6. **Muller C.O.** (Mars 2022), Neuroimagerie fonctionnelle pour la réadaptation post-AVC, activations corticales des mouvements du membre supérieur. *La semaine du cerveau, PhD Pub Montpellier*

7. **Muller C.O.**, Bakhti K.K.A., Muthalib M., Laffont I., Perrey S. (2021) Neural correlates of functional upper limb motor task performance using combined fNIRS-EEG. *19^{ème} Congrès international de l'Association des chercheurs en activités physique (ACAPS)*
8. **Muller C.O.**, Bakhti K.K.A., Muthalib M., Mottet D., Perrey S., Laffont I. (2021) Bilateral motor cortex activation during unilateral reaching and circular proximal upper limb tasks: perspectives for stroke rehabilitation. *36^{ème} congrès de la SOFMER*

Posters

1. **Muller C.O.**, Muthalib M., Dray G., Xu B., Mottet D., Froger J., Delorme M., Perrey S., Laffont I., Bakhti K.K.A. (Juil. 2022) Evaluation of cortical activation during functional movements at baseline of a post-stroke rehabilitation (ReArm project). *Congrès international de la société de médecine physique et de réadaptation (ISPRM)*
2. Fauviaux T., **Muller C.O.**, Faity G., Bakhti K.K.A., Laffont I., Froger J., Mottet D. (2021) Can a circular steering task quantify sensorimotor integration in persons with stroke? *36^{ème} congrès de la société française de médecine physique et de réadaptation (SOFMER)*

Other scientific productions outside the scope of the thesis

Publications

1. Metais, A., **Muller, C. O.**, Boublay, N., Breuil, C., Guillot, A., Daligault, S., Di Rienzo, F., Collet, C., Krolak-Salmon, P., & Saimpont, A. (2022). Anodal tDCS does not enhance the learning of the sequential finger-tapping task by motor imagery practice in healthy older adults. *Frontiers in Aging Neuroscience*, 14, 1060791. <https://doi.org/10.3389/fnagi.2022.1060791>
2. **Muller C.O.**, Metais A., Breuil C., Boublay N., Di Rienzo F., Collet C., Guillot A., Krolak Salmon P., Saimpont A. (*In preparation*) Anodal tDCS does not enhance the effects of motor imagery training of a sequential finger-tapping task in young adults

Communication

1. Métais, A., **Muller, C.O.**, Breuil, C., Boublay, N., Di Rienzo, F., Guillot, A., Collet, C., Krolak-Salmon, P., & Saimpont, A. (2020). P143 Effects of anodal transcranial direct current stimulation combined with motor imagery on motor sequence learning in healthy older adults. *Clinical Neurophysiology*, 131(4), e93–e94. <https://doi.org/10.1016/j.clinph.2019.12.254>
2. **Muller, C.O.**, Breuil, C., Boublay, N., Metais, A., Di Rienzo, F., Guillot, A., Collet, C., Krolak-Salmon, P., & Saimpont, A. (2020). P47 Effects of motor imagery and anodal transcranial direct current stimulation on motor sequence learning in healthy young adults. *Clinical Neurophysiology*, 131(4), e38–e39. <https://doi.org/10.1016/j.clinph.2019.12.158>
3. Metais A., **Muller C.O.**, Breuil C., Boublay N., Di Rienzo F., Collet C., Guillot A., Krolak Salmon P., Saimpont A. (2021) Effects of motor imagery combined with transcranial direct current stimulation on the acquisition of a finger-tapping task in healthy young and older adults. *18ème Congrès international de l'Association des chercheurs en activités physique (ACAPS)*

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List of abbreviations

ANOVA: Analysis of variance	M1: Primary motor cortex
BBT: Box and block test	MEG: Magnetoencephalography
BI: Barthel index	MI: Motor imagery
BOLD: Blood oxygen level dependent	MNI: Montreal neurological institute
CBF: Cerebral blood flow	MP: Mental practice
CBV: Cerebral blood volume	MPAU: Maximal proximal arm use
CIMT: Constraint-induced movement therapy	NVC: Neurovascular coupling
CRUNCH: Compensation-related utilization of neural circuits hypothesis	O₂: Dioxygen
EEG: Electroencephalography	OD: Optical density
ERD: Event-related desynchronization	PANU: Proximal-arm non-use
ERS: Event-related synchronization	PAU: Proximal-arm use
ERSP: Event-related spectrum perturbation	PET: Positron emission tomography
fMRI: Functional magnetic resonance imaging	PFC: Prefrontal cortex
FM-UE: Fugl-Meyer upper extremity	R(e): (effective) Radius
fNIRS: Functional near infrared spectroscopy	rCBF: Regional cerebral blood flow
fTCD: Functional transcranial Doppler	rCBV: Regional cerebral blood volume
HAROLD: Hemispheric asymmetry reduction in older adults	RP: Relative power change
Hb: Hemoglobin	RT: Robot-assisted training
HbO₂: Oxyhemoglobin	SD: Standard deviation
HbR: Deoxyhemoglobin	SM1: Primary sensorimotor cortex
ICA: Independent component analysis	SMA: Supplementary motor area
ID(e): (effective) Index of difficulty	SMC: Sensorimotor cortex
IP(e): (effective) Index of performance	SPAU: Spontaneous proximal arm use
LI: Laterality index	STAC: Scaffolding theory of aging and cognition
LSL: Lab-streaming layer	STFT: Short-term Fourier transform
	tDCS (HD): Transcranial direct current stimulation (high definition)
	UL: Upper limb
	VRT: Virtual reality therapy

W(e): (effective) Width

WHO: World health organization

WMFT: Wolf-motor function test

ΔHbO_2 : Concentration changes in oxyhemoglobin

ΔHbR : Concentration changes in deoxyhemoglobin

Units

°: degree

%: percentage

μmol : micro-mols

μv : micro-volt

cm: centimeter

Hz: Hertz

min: minute

mm: millimeter

ms: millisecond

n: number of subjects in the sample

nv: nano-volt

p: p-value

rs^2 : rho²

s: second

η^2_p : partial eta square

Résumé

L'autonomie d'une personne dépend en partie de sa capacité à réaliser les activités de la vie quotidienne, et cette capacité peut être altérée par le vieillissement et la survenue de pathologies telles que l'accident vasculaire cérébral (AVC). La préservation et/ou la récupération des capacités fonctionnelles sont profondément liées à la plasticité du cerveau. Dans ce contexte, la connaissance de ces réorganisations cérébrales ainsi que de leurs liens avec le mouvement permettrait une meilleure compréhension des effets du vieillissement sain et une meilleure prise en charge de la récupération fonctionnelle post-AVC. L'association de méthodes de neuroimagerie fonctionnelle par électroencéphalographie (EEG) et spectroscopie dans le proche infrarouge (fNIRS) avec l'analyse cinématique du mouvement du membre supérieur (MS) pourraient permettre de mieux comprendre les modifications du mouvement et de l'activité cérébrale lors du vieillissement et après un AVC.

Ce travail de thèse avait trois objectifs : i) développer une méthodologie pour évaluer l'activité cérébrale et la cinématique du mouvement proximal du MS ; puis évaluer les modifications de l'activité cérébrale et du mouvement ii) lors du vieillissement sain et iii) après un AVC.

Pour répondre au premier objectif, nous avons élaboré une méthodologie pour évaluer simultanément l'activité cérébrale et la cinématique de deux tâches fonctionnelles : i) une tâche d'atteinte d'une cible, et ii) une tâche de suivi de trajectoire circulaire impliquant le conflit vitesse-précision. La méthode d'enregistrement de l'activité cérébrale était basée sur l'amplitude (fNIRS) de l'activité du cortex sensorimoteur primaire (SM1) et les modifications de la puissance spectrale de rythmes spécifiques (EEG). Ensuite, deux études expérimentales ont été menées pour décrire les modifications cérébrales et cinématiques au cours des tâches i) et ii), liées au vieillissement sain et à l'AVC. Nous avons constaté que le vieillissement sain entraînait de moins bonnes performances dans la tâche de suivi de trajectoire circulaire, mais aucune modification cinématique dans la tâche d'atteinte. De plus, nous avons identifié une augmentation de l'activité ipsilatérale du SM1 chez les adultes plus âgés dans la tâche de suivi de trajectoire circulaire. Dans un second temps, nous avons mis en évidence une augmentation de l'utilisation du tronc et une réduction de la vitesse de mouvement pour les sujets post-AVC dans les deux tâches. En ce qui concerne l'activité cérébrale, nous avons constaté une augmentation de l'activation du SM1 dans la tâche d'atteinte avec le bras parétique, surtout chez les patients présentant une déficience plus importante et une utilisation accrue des mouvements du tronc.

En conclusion, ce travail a permis de mieux rendre compte des stratégies de compensation/adaptation du cerveau associées aux modifications fonctionnelles du mouvement. D'un point de vue clinique, la perspective majeure de ce travail serait d'identifier les marqueurs d'une récupération fonctionnelle optimale lors de la rééducation post-AVC.

Mots clefs : mouvement du membre supérieur, EEG, fNIRS, cinématique, vieillissement, AVC, cortex sensorimoteur

Abstract

The autonomy of individuals depends on the ability to perform daily-life activities which can be impaired both with aging and the onset of pathologies such as stroke. The preservation and/or recovery of the motor functional abilities are deeply linked to brain plasticity. Thus, a better knowledge of these brain activations reorganisation and how they are linked to functional movement would allow a better understanding of healthy aging effects and a better management of patient's recovery. Association of functional neuroimaging methods such as electroencephalography (EEG) and near-infrared spectroscopy (fNIRS), with kinematic analyses of upper-limb (UL) movement could benefit in the understanding of movement and brain adaptations associated to aging and post-stroke recovery.

In this context, this thesis work aimed were to: i) develop a suitable methodology to evaluate the task-related brain activity coupled with kinematics of UL proximal movement and evaluate the brain and movement modifications ii) in healthy aging and iii) in post-stroke population.

To respond to the first objective, we built an experimental setup to evaluate the task-related brain and kinematics activity during two functional tasks: i) a reaching target task, and ii) a circular steering task capturing the speed-accuracy trade-off. Combine fNIRS-EEG system was used to record the primary sensorimotor (SM1) activity. Then, two experimental studies were carried out to depict the brain and kinematics modifications during the two functional tasks related to healthy aging (2nd objective) and post-stroke (3rd objective). First, we found that healthy aging was leading to poorer performances in the circular steering task, but no kinematics modification in the reaching task. Moreover, we showed an increase SM1 ipsilateral activity in the older adults for the circular steering task. Second, we highlighted trunk use increase and a reduced movement velocity in both tasks for post-stroke patients. Regarding the brain activity, we found an increased SM1 activation during the reaching task with the paretic arm mainly in patients with higher impairment, and an increased use of trunk movements.

In conclusion, our work helped to better delineate the brain compensation/ adaptation strategies associated to functional movement modifications during healthy aging and/or post-stroke. From a clinical point of view, this work opens avenues for the identification of markers of an optimal functional recovery.

Keywords: upper-limb movement; EEG; fNIRS; Kinematics; aging, stroke; sensorimotor cortex

1

PART I - INTRODUCTION

Worldwide aged population is increasing quickly than it used to be, and according to the World Health Organization (WHO), by 2050, people of 60 years old and more will be more numerous as the young teen-adults (15-24 years old) by 2050 (WHO, *Ageing and Health*, 2021). It is a huge public health concern in terms of costs (Mendelson & Schwartz, 1993) as aging is impacting many functions such as motor ones, sensory and cognitive processes and could progressively evolve leading to pathological aging (i.e., physical and mental deterioration that take place due to age-based illness, independently from typical aging modifications). Even in the case of healthy aging (i.e., modifications undergone by an organism when it advances in age, apart from any disease), these different declines occurring with aging affect the autonomy of the elderly in their everyday tasks. Indeed, decrease in motor performance with aging (Seidler et al., 2010) alters more specifically the daily life tasks involving upper limb (UL) movements (e.g. hand control for reaching tasks; Wittenberg et al., 2022). To limit the consequences, and not leading to a poorer quality of life, a society necessity is to adapt the care to prevent the loss of autonomy of the elderly and their dependence to allow them to live independently as long and as well as possible. The aging motor and cognitive functions decrease can go through out pathological aging with for example an increased risk of developing stroke (90% of person touched by stroke are 50 years old or more and 50% have more than 75 years old, Société française neuro-vasculaire).

With a very high prevalence, stroke is the third cause of death and the first cause of acquired disability in adults in well-developed countries. Up to 85% of post-stroke individuals have hemiparesis that affects one side of the UL (Jones, 2017), which results in a reduced ability to use the paretic UL during daily living activities (van Kordelaar et al., 2012) and may lead to permanent disability (Cirstea & Levin, 2000; Nakayama et al., 1994) with sensory-motor and functional physical limitations. Less than 50% recover UL function, particularly hand reaching (Nakayama et al., 1994). These troubles are going to affect the autonomy and quality of life of the post-stroke patients which makes recovery of UL function a real challenge in rehabilitation.

After a stroke, there is a disruption in the interhemispheric balance leading to an underutilization of the damaged hemisphere. In order to optimize rehabilitation in the aftermath of a stroke, it would be interesting to know as precisely as possible the characteristics of the patients' cerebral activations, in comparison to healthy brains and their evolution over time by looking at, functional task-related brain activity. For this purpose, two available non-invasive neuroimaging methods allow for recording the task-related brain activation for bedside use or in field monitoring: functional near-infrared spectroscopy (fNIRS) and electroencephalography

(EEG), respectively based on haemodynamic response and electrical activity of brain regions. Both methods could be associated to lead to a better spatiotemporal cortical activity analysis related to UL tasks to unveil underlying UL recovery mechanisms (Li et al., 2020). We nevertheless have little information on sensorimotor activity during functional tasks involving the entire joint chain of the UL. The ability to use the arm and the non-mandatory compensations of the trunk, assessed by objective kinematic analysis, are also very important aspects of functional motor recovery. Understanding the neural correlates linked with UL functional movements may help to better understand how healthy and pathological aging affect kinematics of movement and related-brain activity, looking to variables such as the level of brain activation and lateralization of the sensorimotor network related to the speed and accuracy of movement (Song et al., 2014; Larivière et al., 2019).

As such, this thesis work aims to measure and better understand the brain activity and kinematics related to UL functional movement by assessing the brain activity modification with healthy aging and pathological aging. This could allow a better follow-up of the patients during stroke rehabilitation and so improve the individualization of the rehabilitation program. Panel 1 is presenting the outline of the literature review we will follow to introduce the theoretical background with 4 main parts: 1) Aging, 2) Improving UL function, 3) Evaluation of UL movement and related brain activity, and 4) Task-related brain activity.

In order to answer to this main objective, this work went through: 1) the development of joint methods to evaluate the task-related brain activity and kinematics of specific functional UL movement, 2) the study of the effect of healthy aging on the task-related brain activity and kinematics of the UL movement; 3) and then the effect of pathological aging (i.e., stroke) on this task-related brain activity and kinematics.

AGING CONTEXT

Chap 1

Worldwide population getting older



↑ UL FUNCTION

Chap 2

Neuroplasticity

Rehabilitation

EVALUATION

Chap 3

Brain

Movement

TASK-RELATED BRAIN ACTIVITY

Chap 4

Healthy young population

Healthy aging

Pathological aging
(i.e., stroke)



Thesis objectives

Chap 5

Panel 1

2

PART II – REVIEW OF LITERATURE

Chapter 1: Aging

With a constantly growing worldwide population and life expectancy, aging is becoming a societal issue, with more and more retired people to support. In France, according to the INSEE (Institut national de la statistique et des études économiques), in 2022, people of more than 60 years old are representing 27.1% of the total population. The aging population growth is a public health concern in terms of costs (Mendelson & Schwartz, 1993) since aging is impacting many functions such as motor ones, sensory and cognitive processes that need to be taken care of the maintained and improved life quality.

Claude Jeandel, French geriatrician, through its paper on the different paths of aging (“*Les différents parcours du vieillissement*”, 2005), presents three possible paths of aging. First, the usual aging, or healthy aging, which is characterised by a reduction of some abilities/function without implication of any disease. Healthy aging could be related to all the modification that are happening for an organism with age growth, without any kind of sickness. It is also called physiological aging and will touch every single human being. It is concerning every level of the human body: genes, molecules, cells, tissues, organs, capabilities. It is a slow and progressive process that is leading to old age condition, and it is accompanied by a decrease in the body's functional capacities. Second, this healthy aging could also be at high level of function (Jeandel, 2005), representing a robust aging, characterized by the maintenance of functional capacities or their very moderate decrease. This robust healthy aging could be related to the definition given by the first WHO (World Health Organisation) Global Strategy and Action Plan on Aging and Health Assembly in May 2016, as being “the process of developing and maintaining functional ability that enables wellbeing in older age” (Michel & Sadana, 2017). General healthy aging will be developed in section 1.1.

The third path of aging presented by Claude Jeandel is the aging with co-morbidity, which is characterised by pathologies, more often chronic, for which ones, the age is only representing a risk factor. This pathological aging will be developed in section 1.2. regarding stroke. It is defined as the physical and mental deterioration that take place due to age-based illness, independently from typical aging modifications. With the age increase, the risk to develop pathology is also increasing and among it, the risk of cardiovascular disease is the most important of all (figure 1; Johnson et al., 2019). In fact, aging is leading to in increased arterial thickening

and stiffness as well as dysfunctional endothelium which results in a risk increase for apparition of atherosclerosis, hypertension and stroke (North & Sinclair, 2012).

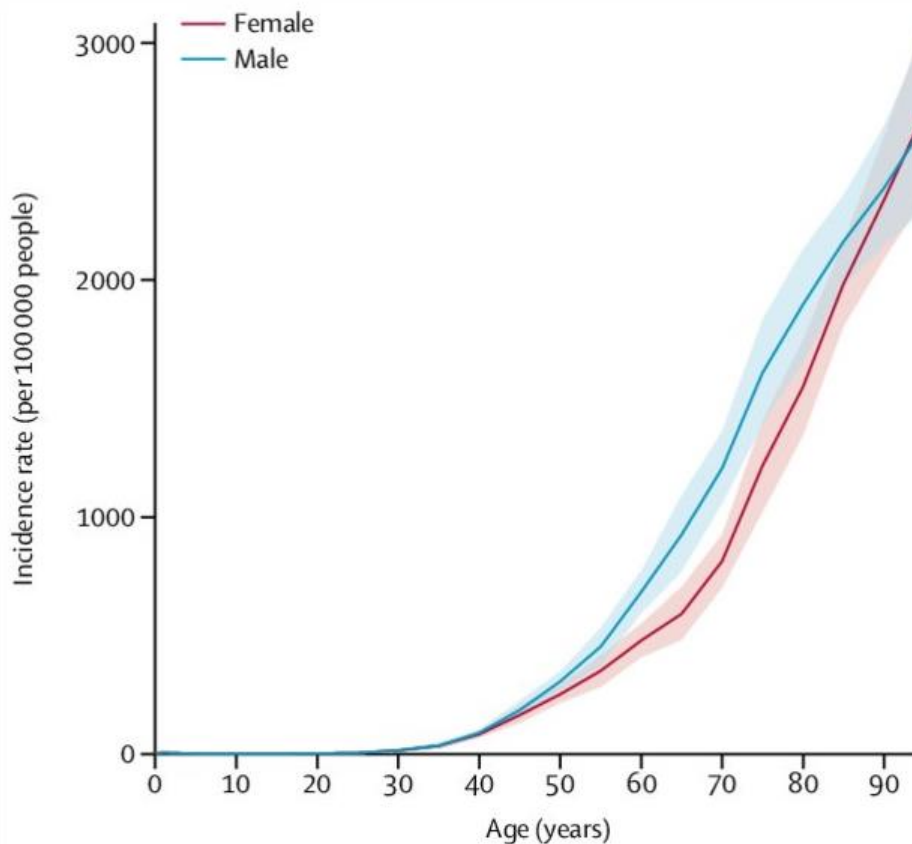


Figure 1 - Stroke incidence with regards to the age and gender.

Figure extracted from a systematic analysis for the Global Burden of Disease group (Johnson et al., 2019)

1.1. Healthy Aging

1.1.1. Physiological modifications

Biological aging is multifactorial and complex process. Aging could be defined as the progressive alteration of the physical, sensitive and cognitive abilities, related to a loss in the physiological integrity (López-Otín et al., 2013).

The molecular characteristics of aging are influenced by genetic, epi-genetic, and environmental factors. All organs are undergone aging effects, but some does more and earlier. This process is creating functional organic difficulties that will progressively perturbate people daily life. At the biological level, it is expressed by the accumulation of molecular and cellular damage, which leads to structural and functional aberrancies in cells and tissues (i.e., loss of mitochondrial homeostasis, impaired, intercellular communication, senescence, decrease

regenerative capacity; López-Otín et al., 2013). It is associated with a reduction in the reparative and regenerative potential in tissues and organs. This reduction manifests as a decreased physiological reserve in response to stress (termed *homeostenosis*) and a time-dependent failure of complex molecular mechanisms that cumulatively create disorder (Khan et al., 2017). The so called homeostenosis process is characterising a reduction in the ability to maintain the homeostasis (i.e., ability of a system to maintain its internal environment balance). For older adults, the ability to come back to homeostasis after a perturbation is reduced (figure 2; Taffett, 2003).

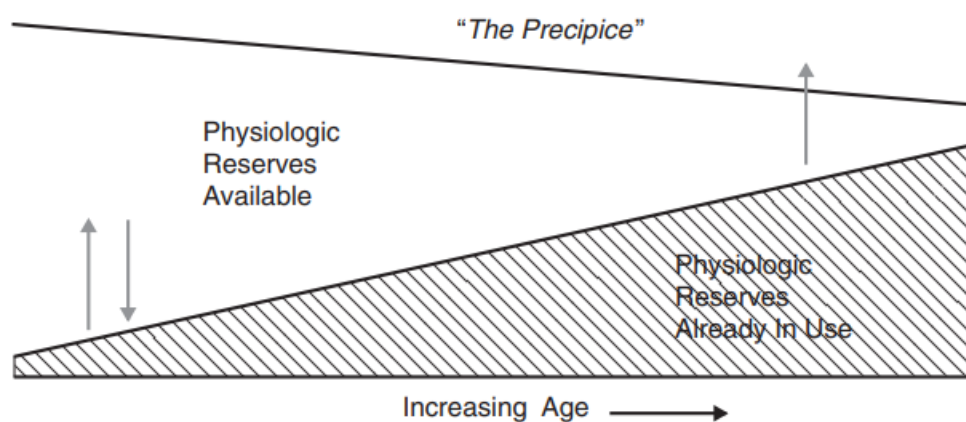


Figure 2 - Schematic view of the homeostenosis process.

The consumption of physiological reserves by the older person is leading to a reduction of the reserves for higher demanding requests. From Taffett et al. (2003).

This aging is mainly related to a cognitive decrease with an alteration of the brain regions sub-tending the cognitive processes. Indeed, with age, density of the white matter in the brain is reduced, leading to a cerebral atrophy (Raz et al., 2005). This atrophy is going to lead to a reduced neuronal network efficiency (Park & Reuter-Lorenz, 2009). This cognitive decline is mainly related to this reduction of brain volume and is increasing after 60 years old (Salthouse, 2009). This neural degradation can be categorized into two sections: “neural challenges” and “functional degradation”. The first one echoes to the primarily structural changes in the brain that occur with age, including loss of white matter, atrophy, loss of mass, etc. The second one is about the indicators of the “maladaptive” brain activity including loss of region specialisation (Park et al., 2004; Voss et al., 2008), decrease memory-related recruitment (Cabeza et al., 2004) and dysregulation of the default mode network (Lustig et al., 2003; for a review see Park & Reuter-Lorenz, 2009).

Linked with the physiological modification induced by aging, we can observe functional ability related modifications.

1.1.2. Functional abilities modifications

Referring to the international classification of functioning, disability, and health (ICF; Svestková, 2008) of the WHO, functional abilities could be related to the “activities and participation” section. Activity is the execution of a task or action by an individual and participation is its involvement in a life situation. More specially, in this model, the activity limitation is related to the difficulties an individual may have to execute activities, and restriction of participation are related to its involvement in life situation.

Functional ability consists of the intrinsic capacity of the individual, relevant environmental characteristics, and the interaction between them. Intrinsic capacity comprises all the mental and physical capacities that a person can draw on and includes their ability to walk, think, see, hear, and remember. The level of intrinsic capacity is influenced by several factors such as the presence of diseases, injuries, and age-related changes. Environments include the home, community, and broader society, and all the factors within them such as the built environment, people and their relationships, attitudes and values, health and social policies, the systems that support them and the services that they implement. Being able to live in environments that support and maintain one’s intrinsic capacity and functional ability is key to healthy ageing.

To follow the function evolution with aging, we have to look to the ones that are fundamentals for the daily life autonomy (e.g., mobility, nutrition, personal care, psychological state, cognition, vision...). They are the one that will provide the biophysiological changes that occur as part of normal aging can impact and limit functional performance in the elderly (Caserta et al., 2009). The extent of impact to functional abilities in the elderly is dependent on numerous factors, including cognitive status, physical disability, and medical illness (Njegovan et al., 2001), as well as, emotional factors, quality of life, and numerous protective factors (Vaillant, 2007). With aging, the associated reduction of abilities is also inducing a lower ability of the organism to adapt to such a situation.

This point is a major key to understand the effect of aging on the social and emotional state of the persons. Indeed, lots of authors have highlighted the link between the loss of function and a reduction of autonomy (Graneheim & Lundman, 2010; McInnis & White, 2001), with for

example reduced ability to move alone, to drive a car (Smith, 2012). These losses (auditory and visual troubles, muscle weakness for instance) and the dependency that is growing would reinforce the loneliness feeling (Graneheim & Lundman, 2010). The functional decrease whether it is related to physical, psychic, and emotional spheres, is thus leading to strong modification in the independency and autonomy of daily living people.

1.1.3. Upper limb functional movement modifications

In addition to cognitive function, person's autonomy goes with the ability to realize everyday life activities such as: getting dressed, reaching objects, eating, drinking, hygienic tasks, and so on with lots of daily life task. This kind of specific movement can be called functional movement, which is, a movement required in daily life, based on real-world conditions within the expected normal range of motion in the human body. It would be thus interesting to look to 'how the functional movement' is affected with healthy aging.

Lots of research have looked through the effect of aging on specific tasks such as visuomotor transformations (Przybyla et al., 2011), handwriting (Birren & Botwinick, 1951; Spirduso, 2005), and drawing using joysticks (Bangert et al., 2010), or digital tablets (Bangert et al., 2010; Poston et al., 2009). They investigated the effect of age on motor learning (Pratt et al., 1994), handedness (Kalisch et al., 2006; Przybyla et al., 2011), bimanual performance (Bangert et al., 2010; Goble et al., 2010; Lee et al., 2002, 2002; Temprado et al., 2010), fine motor control (Kalisch et al., 2006), and proprioception (Adamo et al., 2007; Kaplan et al., 1983). The typically finding of this research is an inferior performance of elderly participants.

Let's now look more precisely into the kinematics of UL functional movement and its evolution with aging. Moving to achieve a functional task, requires coordination, and biomechanical variables ruling the joint arm motion, which are the interaction between muscle torque and inertial resistance (Cesqui et al., 2008). An experimental study has tried to specify the strategy used by healthy older adults on a pointing task and found different motor control strategies to realize the task (Cesqui et al., 2008). Younger subjects seem to firstly minimize the hand path error with a second process of effort optimization, while the older subjects slow down the two mechanisms to optimize kinematic performance and enabling more dynamic adaptation mechanism. Moreover, it has been shown that simultaneous control of shoulder and elbow (necessary for functional aiming task), is less efficient with aging (Seidler et al., 2010). So far, it has been shown that healthy aging leads to kinematics changes in the performance of daily life

activities with increased trial duration and trajectory length (Gulde & Hermsdörfer, 2017; Schaefer, 2015). More recent studies have described the effect of aging on the speed and execution of UL functional movement kinematics (Gulde et al., 2019). Their results suggested that the performance decrease in daily life tasks was particularly caused by age-dependant changes in cognitive capacities.

We just presented the physiological, cognitive, and functional movement modifications that go with healthy aging. Now, we have to consider another type of aging, previously mentioned, the pathological aging and more specially, one of the most prevalent age-related pathologies, the stroke. Indeed, in high-income countries, the main driver for increased stroke prevalence is aging of the population, as age is the most important nonmodifiable risk factor for stroke (Sharrief & Grotta, 2019).

1.2. Pathological aging: the case of stroke

1.2.1. Definition, prevalence, epidemiology

Stroke is a public health problem, recognized as a global epidemic (Béjot et al., 2019). It is the second leading cause of death in the world with 6.7 million deaths/year (after myocardial infarction) (WHO). Because this pathology affects 1 person every 5 seconds in the world, the WHO speaks of a pandemic and projects an increase in the incidence of stroke from 16 million in 2005 to 23 million in 2030. If we look closer on the epidemiology of stroke in France, according to the 2019 INSERM report, stroke is the 1st cause of acquired handicap, the 2nd cause of dementia and the 2nd cause of mortality (1st for women). There is a stroke every 4 minutes and in 40% of the cases there are severe sequels. Stroke can occur at any age: while the average age of stroke is 74 yrs., 25% of patients are under 65 yrs. and 10% under 45 yrs.

Stroke is defined by the WHO as: a sudden loss of focal brain function with no apparent cause other than a vascular cause. It used to be commonly referred to as a "brain attack". It belongs to the group of cardiovascular diseases. Two mechanisms are at the origin of this deficit and make it possible to define the two main types of types of strokes: ischemic and hemorrhagic (more details in the next sub-section).

In spite of rehabilitation, at the end of the treatment process, the percentage of people who remains very physically dependent is 43.2% (Fery-Lemonnier, 2009). Indeed, most survivors have neuro-locomotor, cognitive or psycho-affective after-effects. These sequels will lead to

limitations in activities of daily living, causing a restriction in social participation (Gadidi et al., 2011; Mayo et al., 2002). Stroke is a public health problem that, because of the aging of the population, will become a major concern in the coming decades (Spieler et al., 2003). Financially, this represents an annual expenditure of 3% of the French health budget, with financial impact for the care sector and for the medico-social sector. Institutions are also concerned by this problem: 2% of stays in short-term hospitalization, 4.5% of days in follow-up care and rehabilitation (SSR), and 1.5% of days in long-term care and 5% of people living in residential care facilities for the elderly (EHPAD) are people who have suffered a stroke.

These past 10 years evolutions, with new intervention methods (i.e., thrombectomy, thrombolysis, Cognard et al., 2016) and structuration of care have hugely participated in the limitation of the post-stroke sequels, with a significant improvement in the functional prognostic (Paul & Candelario-Jalil, 2021). But at this time, there is not enough data to assess the extent to which there are fewer patients with severe sequels. Despite medical progresses, stroke is the leading cause of long-term disability and even in the chronic stage (> six months post-stroke), UL paresis is still present in approximately 50-75% of survivors (Kwakkel et al., 2004; Parker et al., 1986).

1.2.2. Physiopathology

Stroke, previously called cerebral infarction, is the result of the privation of nutrients (i.e., glucose, O₂) in a part of the brain, following an occlusion of the arterial network irrigating it. The blood flow is then suddenly reduced, or even cut off, with the following consequences: the death of the tissue's afferent to the area, the formation of a perilesional oedema and the development of parallel circuits to ensure irrigation around the injured region. This decrease in blood flow is caused by a multitude of causes, the most obvious of which are: blood embolism as a result of atheromatous plaque remodelling, cardioembolic malformations, and occlusion of small arteries. This ischemic stroke constitutes about 80% of cases. It is also referred to as cerebral hemorrhage. It occurs after an abnormal passage of blood out of the vessels and thus into the surrounding tissue. The destruction of brain tissue is more rapid in this case. Hemorrhagic stroke represents about 20% of the cases of stroke (Bejot et al., 2008; Caplan, 2011; Gosseume et al., 2016).

Ischemic stroke is caused by the drastic reduction or cessation of blood flow to the brain due to a blockage in a cerebral artery. This blockage is most often caused by thrombotic or embolic occlusion of an artery, which is the blockage of the artery by a blood clot. Smaller

arteries or arteries where there is an accumulation of atheromatous plaque (atherosclerosis) are more prone to occlusion (Giraldo, 2017a). Atherosclerosis is a process in which fatty deposits (atherosclerotic plaque) invade the interior of blood vessels, most often major arteries, and areas of greater vascular turbulence. Atherosclerotic plaque gradually reduces the area available for blood flow, making the vessel more susceptible to thrombosis or embolism. The carotid circuit and small deep cerebral arteries are prime areas for thrombosis and embolism. Blockage of blood flow causes anoxia in the area vascularized by the artery and death of neurons in that area. This results in the loss of brain functions localized in the area usually vascularized by the blocked vessel.

In another hand, hemorrhagic stroke is caused by bleeding into the brain (intracerebral hemorrhage) or bleeding around the brain (subarachnoid hemorrhage) as a result of a ruptured blood vessel. Brain hemorrhages are most often caused by uncontrolled high blood pressure and, in some cases, by abnormalities in the structure of the blood vessels (e.g., aneurysms or vascular malformations). Hemorrhagic stroke is usually found in small atherosclerotic cerebral arteries compromised by chronic hypertension (Giraldo, 2018b). The hemorrhage causes the brain area normally vascularized by the vessel to be deprived of blood supply, and the blood that accumulates outside the vessel causes additional pressure on brain structures, potentially causing anoxia to neurons in surrounding areas.

Stroke victims go through three phases of post-accident evolution beginning directly after the stroke: the acute phase, which lasts for one week; the subacute phase, which lasts for six months, followed by the chronic phase (Alrabghi et al., 2018). The consequences of a stroke vary from person to person depending on the type, severity, location, and number of strokes. The brain is an extremely complex organ that controls various body functions. If a stroke occurs and blood flow cannot reach the region that controls a particular body function, that part of the body would not work as it should. The sequels that patients can present after a stroke are thus really various: motor disabilities; swallowing disorders; dysarthria; aphasia; epilepsy; cognitive decline; hemiplegia; sensitivity troubles; and other invisible disabilities such as fatigue, concentration problems, anxiety or irritability.

We can go back to the ICF model, to describe stroke consequences. The ICF model relies on a disability integrative vision provided by the WHO. In this context, stroke sequels can be related to disabilities and functioning aspects, that arise from interaction between health (disease, injuries, disorders) and contextual factors (Quintas et al., 2012). A comprehensive ICF Core Set for stroke can also be found, as a shorter list of the ICF adapted for stroke case (Geyh et al.,

2004). An example of the selected categories of the component activities and participation is presented in table 1. Here we present just few examples of the body function that could be altered and the results in activities and participation limitations in daily living.

Table 1 - International Classification of Functioning, Disability and Health (ICF).

Examples of the component “body function” and “activities and participation” included in the comprehensive ICF Core Set for stroke (Geyh et al., 2004)

ICF code	ICF section	ICF category title
<i>b710</i>	Body function	Mobility of joint functions
<i>b715</i>	Body function	Stability of joint functions
<i>b730</i>	Body function	Muscle power functions
<i>b740</i>	Body function	Muscle endurance functions
<i>b760</i>	Body function	Control of voluntary movement functions
<i>d440</i>	Activities and participation	Fine hand use
<i>d445</i>	Activities and participation	Hand and arm use
<i>d510</i>	Activities and participation	Washing oneself
<i>d540</i>	Activities and participation	Dressing
<i>d550</i>	Activities and participation	Eating

1.2.3. Upper limb motor deficit...

Paresis is the first deficit resulting from the disturbance of the execution of the motor command. It is the most disabling symptom in the hemiparetic patient. It consists of an inability to generate appropriate levels of force and/or develop fine distal motricity to perform movements, regardless of the preservation of the ability to plan the movement (Bourbonnais & Noven, 1989; Gracies, 2005). Thus, neuromuscular performance is significantly impaired in the controlling (paretic) limb compared to the nonparetic limb (Kleim, 2011; Levin & Hui-Chan, 1994; Svantesson et al., 1999).

Due to its implication in everyday activities, UL motor deficit, or paresis, limits the post-stroke individuals' autonomy in daily life activities and may induce persistent disability (Cirstea & Levin, 2000; Nakayama et al., 1994). The functional impact of stroke is major, as autonomy in activities of daily living depends mainly on the quality of motor recovery, especially in the upper limb (Veerbeek et al., 2014). The consequences of stroke are neurological deficits that appear on the side contralateral to the affected brain area. This results in hemiplegia when the

patient has no motor skills on one side of the body, or hemiparesis when the patient has partial motor skills on one side of the body. It is in this context that a rehabilitation can be set up. Go et al. (2014) mention that over 50% of stroke subjects have severe physical and/or cognitive disabilities. UL paresis appears to be the predominant impairment after stroke and only 10-20% of patients regain full or partial UL function due to the complexity of movements required to perform gestures (Coupar et al., 2012; Sivan et al., 2014).

1.2.4. ...And compensations

After a stroke affecting the sensory-motor areas and pathways, the coordination of functional voluntary movements can be impaired. Adaptations can be developed by the patients to compensate the missing/reduced ability and continue to reach the goal. For example, if we focus on the reaching movement, it can be summarized as the action of leading the hand towards a target. This action may involve the coordination of several muscles and joints of the UL and trunk. In healthy subjects, the trunk contributes to the reaching movement only in the case of targets placed beyond the area corresponding to the length of the arm and clinically towards the end of the movement (Rossi et al., 2002). In stroke subject, the threshold moment in which the trunk is recruited is brought forward, leading the displacement of the trunk in contributing to the movement, even for a target located within the arm's reach (Michaelsen & Levin, 2004). This is the major example of compensatory movement; the patient is going to replace the use of the paretic UL by both the use of the less impaired UL and the trunk. When such compensation persists even if the paretic UL recovered enough to be used, this is called learned non-use (Bakhti et al., 2017; Taub et al., 2006). However, the learned non-use phenomenon is more general than this specific case: it applies to any cases when individuals “forget” how to use their affected body parts and instead overuse compensations. Going back to the reaching movement, excessive early trunk recruitment may be an adaptation of the nervous system during stroke recovery (Roby-Brami et al., 1997, 2003). In the specific case of seated reaching task, trunk compensation can inform about proximal arm use, because the hand is the end effector of the kinematic chain formed by the trunk, the arm and the forearm (Robertson & Roby-Brami, 2011): patients can compensate for under-use of one joint with over-use of another joint, within certain limits. Compensatory involvement of the trunk has also been linked to the severity of the motor deficit or to the degree of spasticity (Cirstea & Levin, 2000). For Levin et al. (2009) concerning this "compensatory trunk strategy" the control of the specific hand movement is limited, and the trunk contributes to its transport from the beginning of the movement. These compensatory strategies

may have a functional role for the most deficient patients, but they can also represent a hindrance to optimal recovery at the individual level for patients with the least deficits.

1.3. Chapter 1 key-points

AGING

- Increase life expectancy and thus elderly
- Increase cardiovascular risk and among all, stroke
- Daily life autonomy could decrease with lower functional abilities
- Healthy aging is leading to functional and physiological modification
- Stroke major alteration, paresis with UL function alteration

- AIM = increase motor function for a better life at home
- How can UL motor function be maintained or recovered?

Panel 2

Chapter 2: Improving UL function: neuroplasticity and rehabilitation

In the previous chapter we presented two major paths of aging, a healthy one and a pathological one regarding a specific case of the most prevalent age-related pathology, stroke. In both cases, we are interested ourselves in the movement to do functional daily life tasks, and how it is affected by aging. Nevertheless, these UL function modifications can be either limited (i.e., in healthy aging by trying to go on a more robust healthy aging) or restored (i.e., in pathological aging through rehabilitation). For both cases, UL function changes will be possible thanks to neuroplasticity phenomena. To illustrate it, this chapter will uncover the notions of neuroplasticity and UL rehabilitation in the context of stroke.

When a pathway, here leading to a brain function, is damaged there are two options to compensate it. Repair the damage or find a way around the damage to get to your destination. In a sense, recovery following a stroke follows this same road. Shortly after a stroke, inflammation of brain tissue begins to clean up some of the damage caused by the stroke. Damaged neurons start the process of healing themselves. Next, for days, weeks and months following stroke the brain takes advantage of its ability to rewire itself, this is neuroplasticity. In essence, neuroplasticity is the mechanism allowing stroke patients to regain lost skills and their autonomy.

Looking to the non-recovery of paretic UL function, it is common affecting more than 80% of stroke survivors making it the primary focus of multiple management (Fuentes et al., 2018). This non-recovery persists beyond 3 months post-stroke, in the subacute and chronic stages (Miller et al., 2010). Although there is no standardized rehabilitation of the paretic UL (Pollock et al., 2014), repetitive task-oriented training has been shown to be effective in improving paretic UL function via neuroplasticity phenomena (Veerbeek et al., 2014). Conversely, non-use of the paretic arm can lead to acquired non-use (Taub et al., 2006), which in turn can drive to brain reorganization (Lindberg et al., 2007) and limit functional movement (Lum et al., 2009) also via neuroplasticity phenomena.

2.1. Neuroplasticity

Neuroplasticity, also known as neural plasticity or brain plasticity, is a process that is leading to reorganisation at the level of the function and the structure within the brain. A good

definition can be “the ability of the nervous system to change its activity in response to intrinsic or extrinsic stimuli by reorganizing its structure, functions, or connections” (Mateos-Aparicio & Rodríguez-Moreno, 2019). Clinically, it is involved in brain modifications that are appearing after injuries such as stroke (Masiero & Carraro, 2008) but also in healthy daily life with brain evolution with age, learning and experience (see Dayan & Cohen, 2011, for a review on motor learning; see Burke & Barnes, 2006 and Guglielmo, 2012, for plasticity in the aging brain). Neuroplasticity phenomena can be splitting into two major levels: i) the neuronal regeneration, that can go to the level of synapsis plasticity and ii) the functional reorganisation (Froger et al., 2017). In stroke, neuroplasticity is the brain’s ability to develop new pathways, change existing pathways or to recruit other areas of the brain to take over the function of the damaged areas (Jones, 2017).

After a stroke, several steps of neuroplasticity are occurring with time dependant apparition (Langhorne et al., 2011; Sophie Su et al., 2016). First, in the early 48 h, the brain attempts to use secondary neuronal networks to maintain function. Then, in the following weeks, the support cells are recruited, and the cortical pathways shift from inhibitory to excitatory ones. New connections are also made during this period. Months after the event, the brain is still evolving to remodel itself via more reorganization around the damages. Innate physiological and anatomical plasticity are important processes that underlie substantial gains in motor function after stroke (Taub et al., 2002) and the combination of task-specific training and general physical exercise is still the gold-standard treatment for post stroke rehabilitation. We earlier talked about the post-stroke paretic arm and how it is impacting daily life activities. As such, the functional UL recovery is a major axis of post-stroke rehabilitation. The functional improvement in the paretic UL is associated with motor relearning and experience-dependent neuroplasticity (Kleim, 2011; Murphy & Corbett, 2009). Because neuroplasticity is experience-dependent, an enriched environment with sensorial, motor, and cognitive stimulation is key to accentuate the recovery, as such stimuli will elicit various modifications within the brain. Figure 3 is presenting the recovery of body function (impairment) and activities (functional abilities) during the rehabilitation process associated to spontaneous and experience-dependent neuroplasticity (Langhorne et al., 2011).

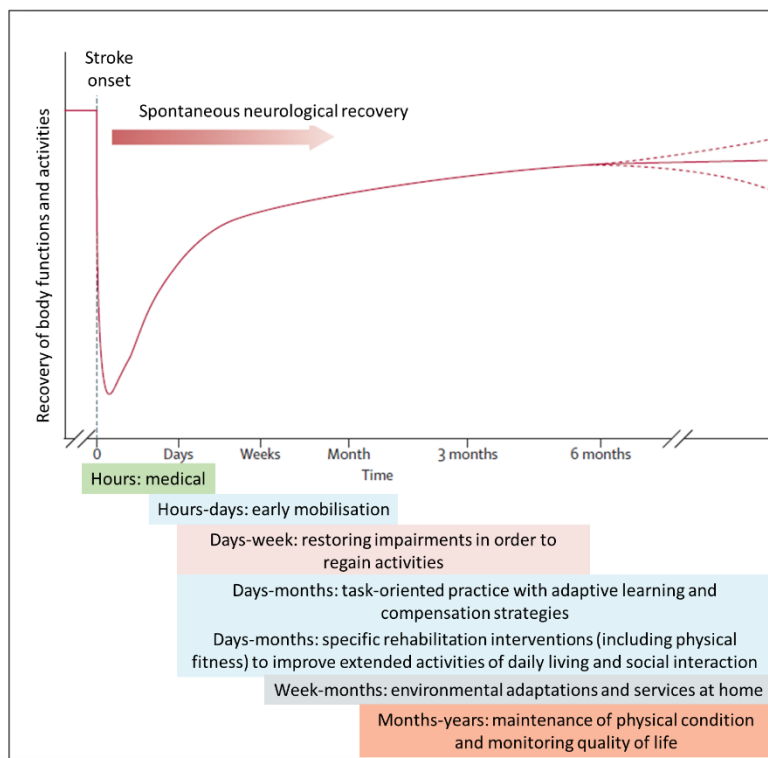


Figure 3 - Theoretical pattern of recovery after stroke with timing of intervention strategies.

In this model, Langhorne et al. (2011) present the timing of recovery associated to rehabilitation. The green box is representing the accident, for the rehabilitation orientation, blue boxes are targeting activities limitations, the pink one body function and structure (impairment), and finally the orange block participation restriction.

Figure from Langhorne et al. (2011)

2.2. The example of post-stroke rehabilitation

Functional improvement in the paretic UL is associated with motor relearning and experience-dependent neuroplasticity (Murphy & Corbett, 2009). There are specific factors related to relearning and neuroplasticity relevant to UL recovery after stroke such as: practice intensity, specificity, variability, motivation, biofeedback... (Kleim & Jones, 2008; Subramanian et al., 2013). Strategies specifically oriented to promoting brain plasticity should be more reinforced in stroke rehabilitation and research. Therefore, it is important to carefully target methods that may have the best impact on post-stroke induced brain plasticity. Table 2 is presenting an overview of few rehabilitation methods that showed positive effects on the UL functional recovery. Moreover, below, we present two examples of neurorehabilitation methods that can be added to conventional therapy whose effects on the neuroplasticity occurrence has been studied: virtual reality therapy (VRT) and non-invasive brain stimulation.

2.2.1. Virtual reality therapy

In the aforementioned context, VRT appears a promising method. It consists in proposing a computer interface through which the patient can interact live, and thus set up the most adapted therapy, both intensive and motivating. VRT (embracing virtual reality and interactive video games) can be defined as "the use of interactive simulations created with computer hardware and software to present users with opportunities to engage in environments similar to real objects and events" (Weiss et al., 2006). The principle of this therapy is that the computer generates a "natural" environment and provides real-time feedback on movements and performance evolution (Levin et al., 2015). This feedback on motor abilities allows for activation of the lesioned hemisphere thus promoting relearning (Sveistrup, 2004). The use of VRT may be an advantage in stroke rehabilitation due to its potential to provide an enriched environment and task-specific repetitive practice (Laver et al., 2015), both of which are important conditions for inducing neuroplastic changes (Hubbard et al., 2009). Moreover, VRT allows for simulated practice of functional tasks at a higher intensity than traditional therapies in stroke rehabilitation (Demain et al., 2013; Kwakkel et al., 2004; Teo et al., 2016). To sum-up, VRT provides specific, intensive, repeated, and motivating therapy with real-time feedback of movements produced and indicators of performance (Levin et al., 2015), which may promote activity-dependent brain neuroplasticity and thus functional recovery. This method, when associated with conventional rehabilitation provides good results on the post-stroke UL functional recovery (see Laffont et al., 2020 showing the main effects of VRT on sensorimotor recovery; and for reviews, see Laver et al., 2015; Mekbib et al., 2020).

2.2.2. Non-invasive brain stimulation

On the other hand, non-invasive brain stimulation, has the ability to modulate neuronal synapses and generates new neuronal associations, leading to neuroplasticity (Schabrun & Chipchase, 2012). Among non-invasive brain stimulation techniques, stimulation with weak direct currents (transcranial direct current stimulation - tDCS) has been shown to induce brain plasticity (Pell et al., 2011) and is increasingly used in rehabilitation. Indeed, the use of tDCS in motor learning has increased dramatically since 2000 (Buch et al., 2017). This method is simple, reliable, inexpensive, and has great potential for use in rehabilitation. TDCS is a non-invasive brain stimulation method that allows for modification of cortical excitability by sending a low-intensity current to the scalp (Thibaut et al., 2013). It has been shown that tDCS with a current intensity around 2 mA for 20-40 minutes did not show adverse effects on post-stroke subjects

during one or more sessions (Chhatbar et al., 2017). It does not present risk to induce undesirable effects (such as epileptic seizures) and could potentially be prescribed for use in the patient's home (Bikson et al., 2016; Nitsche & Paulus, 2011). The clinical efficacy of tDCS has been shown for several conditions such as motor rehabilitation after stroke (Fregni et al., 2005, 2006; Hummel et al., 2005).

There are two types of stimulation, anodal (excitatory) and cathodal (inhibitory), the principle of which is to increase or decrease the spontaneous neuron discharge frequencies and the cortical excitability of the stimulation area, respectively (Nitsche & Paulus, 2011). In the long term, with anodal tDCS, a neuroplastic potentiation phenomenon can be observed. In turn, cathodal stimulation may lead to synaptic depression. In post-stroke patients, it has been shown that anodal stimulation of the ipsilesional primary motor cortex (M1) can improve motor functions (Bolognini et al., 2009). These authors showed that when stimulation was combined with conventional rehabilitation there was an increase in plasticity induced by rehabilitation associated with greater and lasting clinical gains. More recently, it has been shown that the effect of tDCS was greater when it was more focused using several small electrodes (Chhatbar et al., 2017), this type of system being referred to as high definition (HD-tDCS). Thus, tDCS would enhance the brain plasticity mechanisms that occur after a stroke through its neuro-modulatory effect and thus promote functional recovery (Flöel, 2014).

To sum up, this non-recovery of function of the paretic UL is, by its prevalence, the main object of multiple management beyond 3 months post-stroke, at the subacute and then chronic stage, in other words at the end of intensive rehabilitation (Miller et al., 2010). There are multiples UL rehabilitation methods that are already validated (e.g., induced constraint, VRT) or currently in research stage (i.e., neurostimulation, combination of methods, ...). At the end, the global aim is to give back to the patient the highest autonomy possible.

Table 2 – Overview of some rehabilitation methods

Review(s)	Definition of the method	Main results
<p><i>Robotic-assisted training (RT)</i></p> <p>Morone et al., 2020</p> <p>Wu et al., 2021</p>	<p>RT are “devices assisting arm movements or providing resistance during training” (Rabadi et al., 2008)</p> <p>They can provide a “passive movements of the patient’s arm if he/she cannot control it” (Fazekas et al., 2007)</p>	<ul style="list-style-type: none"> + RT is an effective intervention for improving upper extremity motor impairment in stroke patients + Results suggest a better effect of robot-therapy associated to conventional one + Poststroke patients with limited potential for spontaneous recovery may obtain more benefits from RT than from conventional rehabilitation - Finding on robots that self-adapt to patients - Move towards even more automatic models to free the therapist to attend to other patients at the same time
<p><i>Mental imagery (MI)</i></p> <p><i>Mental practice (MP)</i></p> <p>López et al., 2019</p>	<p>MI is a dynamic process in which a movement is mentally simulated without being physically executed (Jeannerod & Decety, 1995)</p> <p>MP based on MI is defined as the rehearsal of an imagined action in order to improve its execution (Jackson et al., 2001)</p>	<ul style="list-style-type: none"> + MP combined with conventional rehabilitation is an effective method for the recovery of functional movement after stroke - MI and MP methods present a great heterogeneity in literature
<p><i>Constraint-induced movement therapy (CIMT)</i></p> <p>Kwakkel et al., 2015</p> <p>Wang et al., 2022</p>	<p>CIMT is a method aiming to improve the function of the affected UL after a stroke by restricting the use of the healthy limb and forcing the use of the affected side.</p>	<ul style="list-style-type: none"> + Can improve the limb function of stroke patients + Positive effect on angiogenesis and nerve regeneration - Requirements regarding muscle strength, muscle tone, and range of motion - CIMT can only be applied in certain conditions, limiting its wide clinical application.

2.2. Chapter 2 key-points

IMPROVING UL FUNCTION

- Neuroplasticity has a major role in both aging paths to limit the UL function limitation or to stimulate the restoration of UL function
- Post-stroke UL recovery relies on motor relearning and experience-dependent neuroplasticity
- UL recovery process can be accelerated using for example: virtual reality environment or non-invasive brain electrical stimulation

- AIM = promote neuroplasticity to increase UL function
- How can UL function and neuroplasticity be evaluated?

Panel 3

Chapter 3: How to evaluate brain and movement functional related activity?

We previously mentioned the close link between neuroplasticity and UL function recovery. Thus, a good way to better understand and maybe classify post-stroke functional recovery will be to evaluate at the same time the functional movement and the related-brain activity. Firstly, to assess the UL function, there are several clinical tests that provide a subjective evaluation of post-stroke movement and function. One of the most reliable of all is the Wolf Motor Function Test (WMFT; Wolf et al., 2001) that quantifies the functional ability of the UL through 15 timed and function-based tasks (i.e., holding a pen, collect paper clips, prehension test) and 2 strength-based tasks (arm lifting and hand grip). Other clinical scores can give information about the elementary motricity and deficiency (Fugl-Meyer, FM; Fugl-Meyer et al., 1975) or gross grasping abilities (Box and Block test, BBT; Mathiowetz et al., 1985). Nevertheless, the clinical tests are limited for the evaluation of brain-movement relationship and are fully relying on the individual therapist judgement. Indeed, the accuracy of the evaluation is time-dependant, not all therapists will spend the same time on it and thus, it could lead to a lack of replicability as there is an inter-observatory variability, and these methods are sensitives to observatory change. Finally, as it will be developed in this section the use of functional neuroimaging methods to monitor brain activity during movement needs some movement specificity (i.e., replication of movement as in block design paradigm) and is not the easiest to do during clinical tests. Thus, to provide precise and quick information about “how” the movement is done, the kinematics method seems relevant as it is allowing a precise evaluation of movement variables such as speed, acceleration, jerk, accuracy, trajectory, movement amplitude, ... (Subramanian et al., 2010).

3.1. Kinematics

At the function level, recovery requires that the task is performed using the same body part and joints in the same movement patterns typically used by non-disabled / healthy individuals (Buma et al., 2010; Levin et al., 2009); while capacity is defined as the highest level of functioning (Lemmens et al., 2012). A classical way to evaluate post-stroke function is to refer to clinical assessments. Nevertheless, clinical assessments can be limited as they are not always able to distinguish recovery from the “way” the movement is done (i.e., *is the patient fully using*

her/his paretic arm? is he/she using trunk compensations? ...). In this context, a new way in evaluating the motor function can be found in the kinematics assessment.

Kinematics movement quality measures are considered valid and sensitive for recognizing UL impairments of post-stroke individuals performing reach-to-grasp tasks (Bakhti et al., 2017; Subramanian et al., 2010; van Dokkum et al., 2014). In these studies, several kinematics variables were extracted for some anatomical points (hand, elbow, shoulder, trunk) thanks to motion capture system: a) movement time; b) mean, peak velocity and number of velocity peaks; c) displacement and trajectory (Subramanian et al., 2010; Van Dokkum et al., 2014; Bakhti et al., 2017).; d) range of motion (Subramanian et al., 2010); e) movement irregularity (Van Dokkum et al., 2014) or else; f) proximal arm use (Bakhti et al., 2017). Moreover, kinematics variables are suggested to be valid for differentiating compensation from recovery and for measurement of UL functional impairment (Shishov et al., 2017; Subramanian et al., 2010). For example, reaching movements are characterized by lack of spatiotemporal coordination between the arm and the trunk (Roby-Brami et al., 1997). The latter study indicated that post-stroke individuals use a new pattern of coordination represented by more trunk recruitment during reaching tasks.

Usually, the motion analysis devices use marker-based systems (Bonnechère et al., 2014). Nevertheless, for rapid, clinically usable evaluation with less time and cost, it appears interesting to focus on an easier way to capture movement in post-stroke population using Microsoft's Kinect (V2 for Xbox One) for example (Bakhti et al., 2018). Indeed, recent numeric development led to the use of marker-less infrared sensors with Kinect allowing a real time tracking of movement (Eltoukhy et al., 2017; Knippenberg et al., 2017). The Kinect is really suitable as it is low-cost and provides good reliability on the tracking of body joint in real-time without any marker. Microsoft develops the tool with a software development kit (SDK) allowing the Kinect sensor to be used as a measurement system. Finally, Kinect sensor is very promising and was validating for UL movement in comparison with a highly accurate 3-D motion capture (Vicon; Bakhti et al., 2018; Kuster et al., 2016).

3.2. Sensorimotor function and neuroimaging

3.2.1. Neuroimaging methods

Neuronal interconnections constitute the primary means of information transmission within the brain and are, therefore, strongly related to the way the brain functions (Smith et al.,

2013). Analysing brain network connectivity from a theoretical point of view has shown significant potential for identifying organisational principles in the brain and their connections to cognitive processes and brain disorders (Bassett et al., 2018; Smith et al., 2009; Supekar et al., 2008). This allows to study the brain and its function from a new perspective that accounts for the complexity of its architecture. To record the brain activity during movement we will talk about functional neuroimaging as its aim is to study the functioning of the human brain during a task or some activity (Raichle, 2009). The functional neuroimaging methods differ in as much as they could record directly neuronal activity or indirectly associated hemodynamic or metabolic activity. Usually, the functional neuroimaging consists of realising a motor or/and cognitive task and recording the outgoing brain activity. Depending on the type of method used, it is possible to identify with more or less spatial (minimum distance that can be measured) and temporal (minimum time that can be measured) resolution, the brain areas activated. The figure 4 is providing a classification of the different neuroimaging methods regarding to their spatiotemporal resolutions (Parasuraman & Caggiano, 2005).

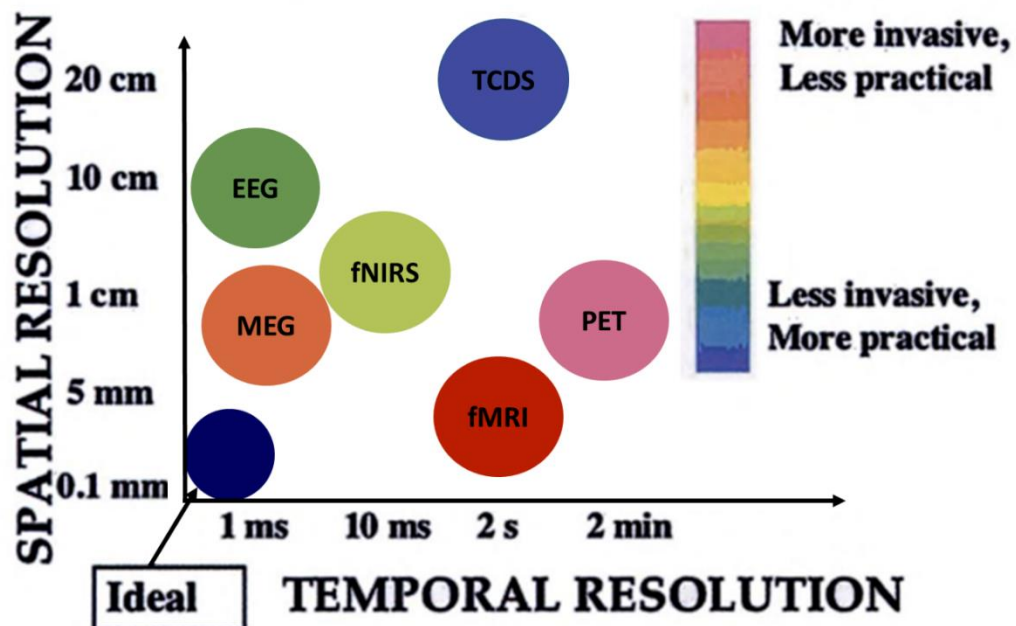


Figure 4 - Comparison of different neuroimaging methods.

Illustration of the compromise between spatial resolution (axis Y) and temporal resolution (axis X) to record the brain activity. The color scale represents the characteristics of the methods, whether they are more or less invasive and practical. The blue circle named 'ideal' is representing the ideal solution for a neuroimaging tool. EEG: electroencephalography; MEG: magnetoencephalography; PET: positron emission tomography; fMRI: functional magnetic resonance imaging, fTCD: functional transcranial Doppler ultrasonography; fNIRS: functional near-infrared spectroscopy. Figure adapted from Parasuraman and Caggiano (2005).

Lots of functional neuroimaging methods have been used to explore cortical plasticity and to monitor functional modification in healthy or pathological populations (Cirillo et al., 2019). In stroke population, functional magnetic resonance imaging (fMRI) represents the most widely used clinical application for mapping functions in the brain (Castellano et al., 2017). In the last two decades, results from a large body of fMRI studies in stroke patients have substantially advanced the current knowledge of brain plasticity mechanisms. With a good spatial resolution of the order of a millimetre, fMRI allows to determine the brain regions activated during a motor task for example. By using the BOLD (Blood Oxygenation Level Dependent) signal, fMRI makes it possible to follow the hemodynamic modifications induced by neuronal activity during the performance of cognitive or motor tasks. In particular, it has been shown that during post-stroke rehabilitation, there is a relationship between brain reorganizations and functional recovery of the paretic arm (Dong et al., 2006). A review evaluating the use of fMRI as a post-stroke prognostic tool found that monitoring brain reorganization provides a better understanding of the course of stroke at different stages, and to better predict patient response to treatment and rehabilitation (Gale & Pearson, 2012).

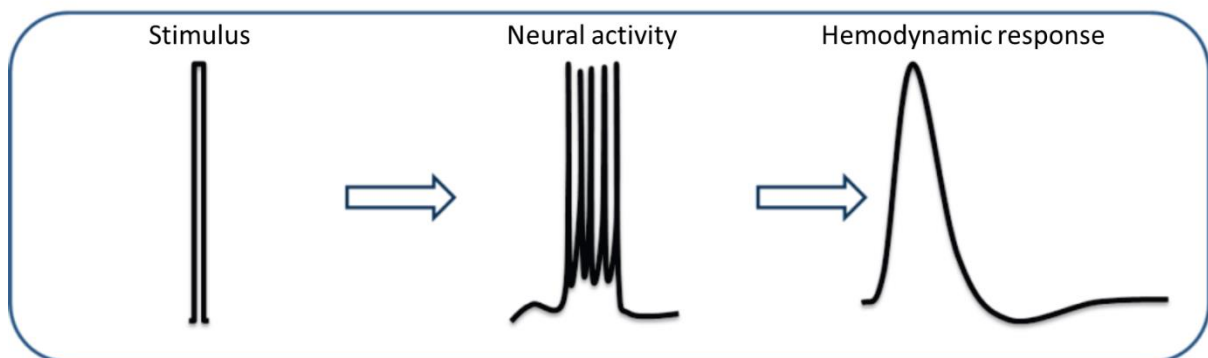


Figure 5 - Illustration of the neurovascular coupling.

When a stimulus is treated, a group of neurons is activated, leading to action potentials, and to hemodynamic response. *Figure adapted from Friston et al. (1995ab).*

To understand how brain signal is recording in fMRI, we must firstly look to the neurovascular coupling functioning (NVC). The NVC is explaining the interaction between the electrical neural activity (excitatory or inhibitory), the cerebral blood flow (hemodynamic) and the energy consumption (metabolic aspect) by the brain tissues (Muellbacher et al., 2002). The consumption of this energy is leading to a vascular response around the region to support the neuronal cells. NVC is leading, in the brain regions, to hemodynamic changes reflecting the electrical activity, and traducing by an excessive increase in local blood flow (Fox et al., 1988;

Lloyd-Fox et al., 2010; Ogawa et al., 1992). The rapid sequence, after a stimulus, of electrical response (within few milliseconds) and hemodynamic one (within few seconds), has been modeled by Friston et al. (1994, 1995); see figure 5).

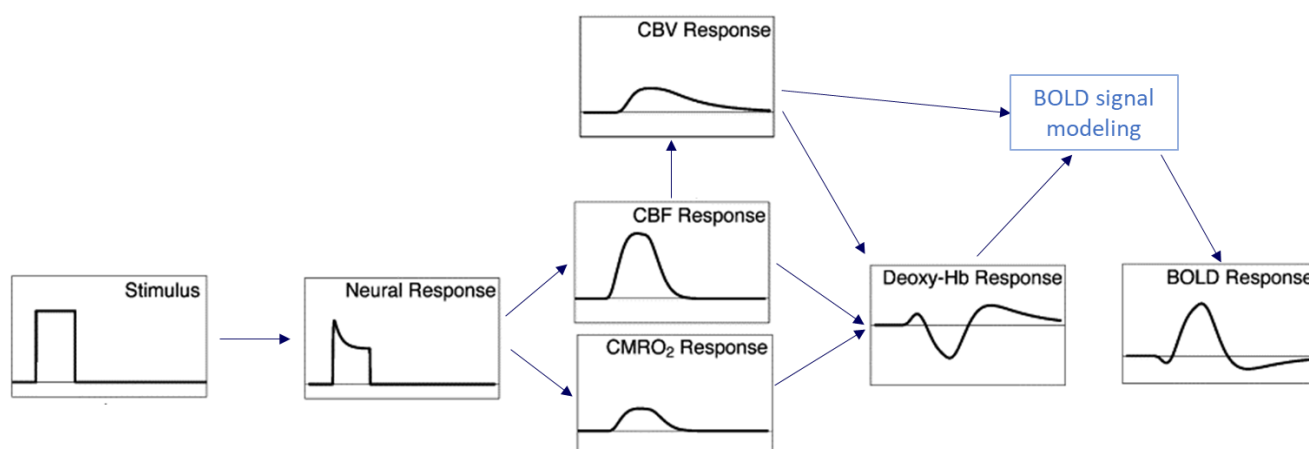


Figure 6 - Model of the BOLD response in fMRI. “Balloon model” of Buxton.

This model is describing at the same time the metabolic response and hemodynamic response following the activity of the neurons and astrocytes. From left to right: a stimulus is leading to a neuronal activity; it is conducting to a slight increase in the local oxygen consumption (CMRO₂); and at the same time an important increase of the cerebral blood flow (CBF); the last two processes are leading to an increase of deoxyhemoglobin (Deoxy-Hb) concentration and of the volume of the vascular balloon. Then modeling of the BOLD response is possible.

Figure adapted from Buxton (2012)

In fMRI, this hemodynamic response is recorded through the BOLD signal. The model the most use to present BOLD signal is the balloon model (Buxton, 2012, see figure 6). This model, in short term, is simplifying the neurovascular dynamic as a coupling between neural activity and evolution in regional cerebral blood flow and volume (rCBF and rCBV, respectively) and the local consumption in oxygen (CMRO₂). This model is presented in figure 6. When the areas are activated by a task, there is the presence of a slight increase in CRMO₂ by neurons that is largely compensated by an increased rCBF. This results in a decrease in the concentration of deoxyhemoglobin (HbR) detectable by its peculiar magnetization (i.e., non-oxygenated blood has a strong magnetic susceptibility in contrast to its opposite) and a slight increase of rCBV (Villringer, 2012).

However, fMRI has several limitations: low temporal resolution, very high cost, need for almost total immobilization of the patient in a lying position (see table 1 in Wallois et al., 2012), for more advantages and limits comparison in between several neuroimaging methods). As a result, the tasks that can be performed under fMRI are not very functional (e.g., thumb-finger opposition task), whereas in the context of post-stroke rehabilitation, we are more interested in movements involving the upper limb as a whole (i.e., wrist, elbow, shoulder) in a sitting/standing

posture that would approximate functional tasks used in daily life (e.g., grabbing a cup). Thus, fMRI is not suitable for rapid measurement of (routine) brain activity to guide clinical management. In this context, we are going to interest ourselves in other functional neuroimaging methods that can counteract the limits of fMRI.

Among the possibilities, let us retain two adapted wearable neuroimaging methods at the bedside. Research has shown that fNIRS was an appropriate substitute for fMRI to study cortical activity during cognitive and motor tasks (Kato et al., 2002; Muthalib et al., 2013; Steinbrink et al., 2006). In another hand, EEG also present lots of advantages to be used as an easy functional neuroimaging method in ecological condition. These two portable methods have been used a lot to investigate brain activity during physical exercises in relatively unconstrained environments (Li et al., 2022; Perrey & Besson, 2018; Tan & Le, 2020; Yeung & Chu, 2022).

3.2.2. fNIRS

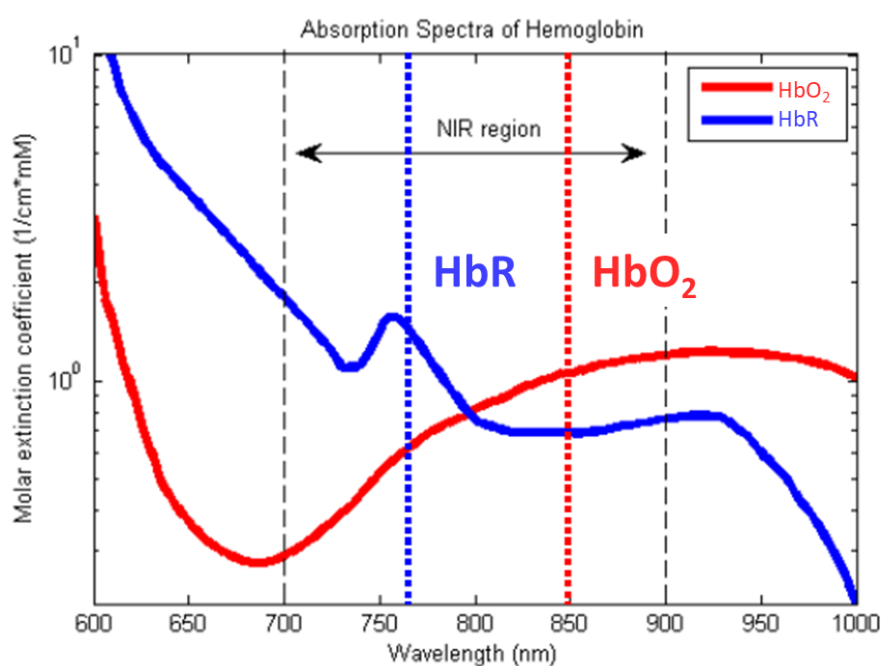


Figure 7 - fNIRS optical window.

Absorption spectra of oxyhemoglobin (red line) and deoxyhemoglobin (blue line) in the near-infrared wavelength (NIR)

Functional near-infrared spectroscopy (fNIRS) is a functional neuroimaging method that is allowing a non-invasive collection of brain hemodynamic signals in an ecological environment during the realization of a functional motor task. Based on the discover of Jöbsis (1977) on the relationship between the intensity of the light, the light absorption and the oxygenation in the brain tissues, this optical method is using light emitted by lasers or LEDs at particular

wavelengths (650-950 nm; see figure 7) to record changes in the CBV and oxygenation linked with cortical activity (Perrey, 2008). The fNIRS method is relying on the properties of the scalp, hair and meninges surrounding the brain areas to absorb and scatter the photons of the near-infrared light that could penetrate the cortex. The idea is that hemoglobin molecule has specific properties of light absorption and scattering. With a transmission of light at the level of a brain region, it is thus possible to evaluate the variation of the hemodynamic and the local blood oxygenation and deduce in turn the related neuronal activity (Huppert et al., 2006; Obrig et al., 2000; Strangman et al., 2006; Villringer & Chance, 1997).

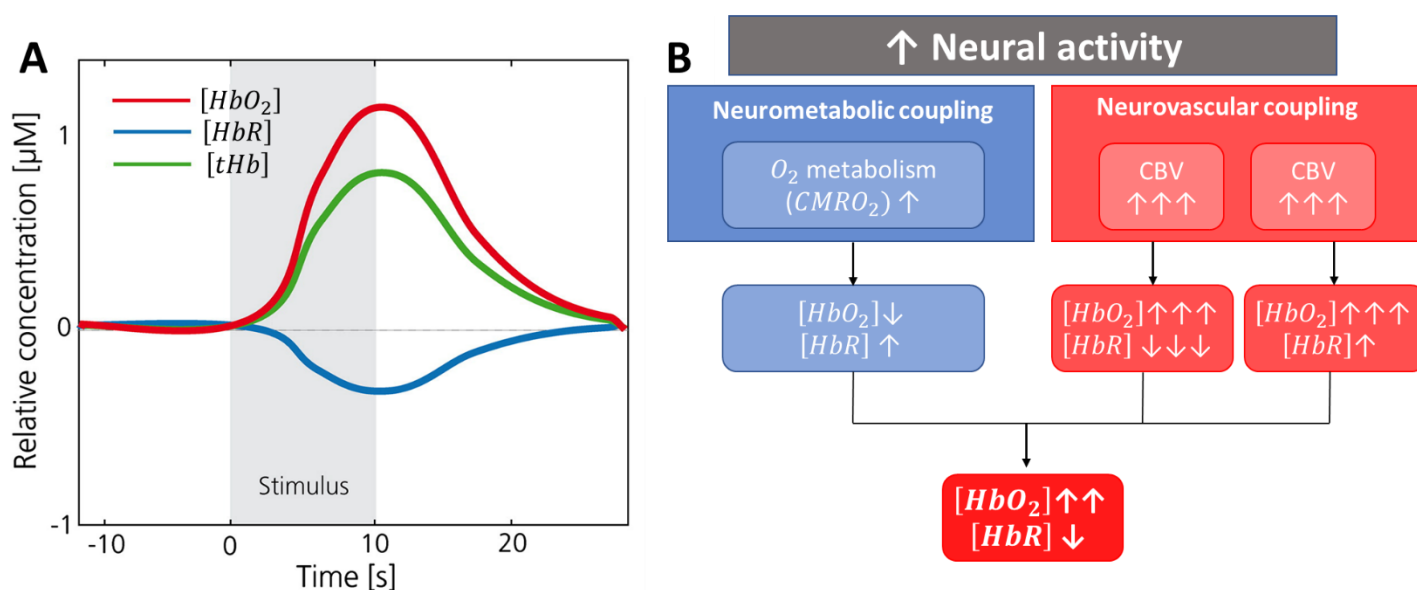


Figure 8 - Schematic illustration of fNIRS recorded physiological reaction.

- A) Typical evoked changes in cerebral oxygenation and hemodynamic due to an increase in brain activity; B) Neurometabolic and neurovascular coupling cerebral hemodynamic and oxygenation changes and their effect on the fNIRS signals in case of an increased neural activity ($[HbO_2]$ Oxyhemoglobin concentration, $[HbR]$ deoxyhemoglobin concentration, $[tHb]$ total hemoglobin concentration).

Adapted from Scholkmann et al. (2014)

fNIRS method is relying on the physiological processes of neurometabolic and NVC (Herold et al., 2020; Scholkmann et al., 2014; see figure 8 for an illustration). In practice, when a task is realized, it causes a higher neural activation in specific brain regions. First, to respond to the energetic demand of the neuronal tissues, the oxygen metabolism is increased (neurometabolic coupling), and there is an increase in the oxygen consumption. Thus, the local concentration of HbO_2 is decreasing while the concentration in HbR is increasing. Nevertheless, the increase in neural activity is also leading to modification in brain hemodynamic, mostly inducing an increase in the blood flow to the activated brain regions. The increase in rCBF is leading to a greater local demand of oxygen than its metabolization, which leads to an increase

in the concentration of HbO₂ and a decrease in HbR concentration (Herold et al., 2020; Pinti et al., 2020; Scholkmann et al., 2014).

fNIRS has a lower spatial resolution than fMRI, but it has the advantage of having a better temporal resolution than fMRI (less than one second, see Figure 6). fNIRS is very interesting in rehabilitation because it allows an ecological situation (standing, sitting) during tasks involving the whole articular chain of the upper limb, it is inexpensive and easy to use, which makes it ideal for use by therapists during routine clinical examinations. Finally, it has been shown that fNIRS was a reliable tool (Strangman et al., 2006) and does not pose a risk to patients (Yang et al., 2019a). This method has been used to measure sensorimotor network activation during UL movements in healthy young adults (Derosière et al., 2014; Nishiyori et al., 2016), in older healthy adults (Kawai et al., 2020; Zhang et al., 2021) and in pathological older adults (i.e. stroke; Delorme et al., 2019; Lim & Eng, 2019).

This neuroimaging method therefore allows monitoring of the follow up of post-stroke cerebral activations of the motor cortex (reorganization) during the functional recovery of the paretic upper limb (Delorme et al., 2019; Lim & Eng, 2019; Mihara & Miyai, 2016; Takeda et al., 2007; Yang et al., 2019).

3.2.3. EEG

Electroencephalography (EEG) measures functional brain activity directly by detecting the variations of electrical currents at the scalp from local electric fields produced by neuronal activity (Olejniczak, 2006) and records frequencies bands from 0.1 Hz to 60 Hz (Brookhuis & de Waard, 2010). The frequencies bands recorded are related to specific states: i) delta waves (1 to 4 Hz) corresponding to deep sleep; ii) theta waves (5 to 7 Hz) corresponding to drowsiness and memory processes; iii) alpha waves (8 to 12 Hz) corresponding to relaxation with eyes opened or closed; iv) beta waves (13 to 35 Hz) corresponding to phase of alertness, concentration or anxiety, intellectual activity, engagement in mental tasks; and finally, v) gamma waves (beyond 35 Hz) corresponding to intense mental activity and motor functions (Holm, 2010). Each wave presents specific amplitude and frequency. The electroencephalogram, resulting from an EEG recording, is the result of the summation of inhibitory and excitatory postsynaptic potentials, mostly in pyramidal cells, occurring in the cortex. Because the electrical fields generated by neurons are attenuated over distance, only the cortical layers near the scalp can influence the EEG signals (Keenan et al., 2013).

The analysis of brain electrical scalp activity is looking either to the mean spontaneous EEG frequency spectrum under various condition, or to the measure of mean of precisely synchronized brain response evoked by discrete experimental stimuli or external events. Due to the low amplitude of the evoked responses recorded over the scalp surface, several trials are required. Indeed, the rhythmic or almost rhythmic activity that is not exactly synchronized with the experimental events is removed and the coherent activity remaining is the event-related potential. When studying event-related EEG activity, amplitude and phase could be considered separately or together. A good example of amplitude change is the reduction occurring in the occipital alpha-band when the eyes are opened. These event-related attenuations in the alpha-band were first studied and named event-related desynchronization (ERD, see figure 9 1-A and 1-B) by Pfurtscheller (1977). This name is originated from the fact that the cortical excitability is relying on the “desynchronization” of the rather slow rhythms and their replacement by faster and more spatially differentiated ones. Authors agreed that desynchronized EEG represents an activated level of cortical neurons (Steriade et al., 1991). Thus, ERD can be interpreted as an electrophysiological correlate of an increased cortical excitability or an activated cortical area. Historically, the ERD analysis was firstly used to quantify the level of desynchronization of the ongoing (“synchronized”) EEG alpha following arousing events (Pfurtscheller & Klimesch, 1991). Thereafter, Pfurtscheller (1992) proposed the term of synchronization for the increase in the time-related rhythm amplitude. A desynchronized system is representing a state of maximal readiness and a maximum of information capacity (Thatcher et al., 1986). For example, desynchronized occipital alpha rhythm is linked to the process of visual information and a desynchronized alpha-mu rhythm (alpha wave in the sensorimotor area) is characteristic of motor behaviour. Another example is the alpha desynchronization for mental task of mathematics calculation (Holm, 2010; Ryu & Myung, 2005).

On the other hand, the opposite phenomenon is the event-related synchronization (ERS, see figure 9 2-A and 2-B), produced by a localized increasing of the alpha and beta waves amplitude with bursts (Pfurtscheller & Klimesch, 1991). Large amplitude of synchronized alpha wave can represent cerebral states where the information processing is reduced, and motor behaviour is null. The brain, or a neuronal system, could be in ‘idling’ mode, meaning there are large amplitudes waves in cortical zones that ‘do not need to do anything’ (Pfurtscheller, 2001). Thus, alpha ERS could be considered as being the result of de-activated neuronal network. In conclusion, looking to the electrical modification of the alpha rhythm, a higher power of the

rhythm spectra is linked to a weak brain activity, and conversely, a weak power is associated to an important cortical activity (Ekkekakis, 2009).

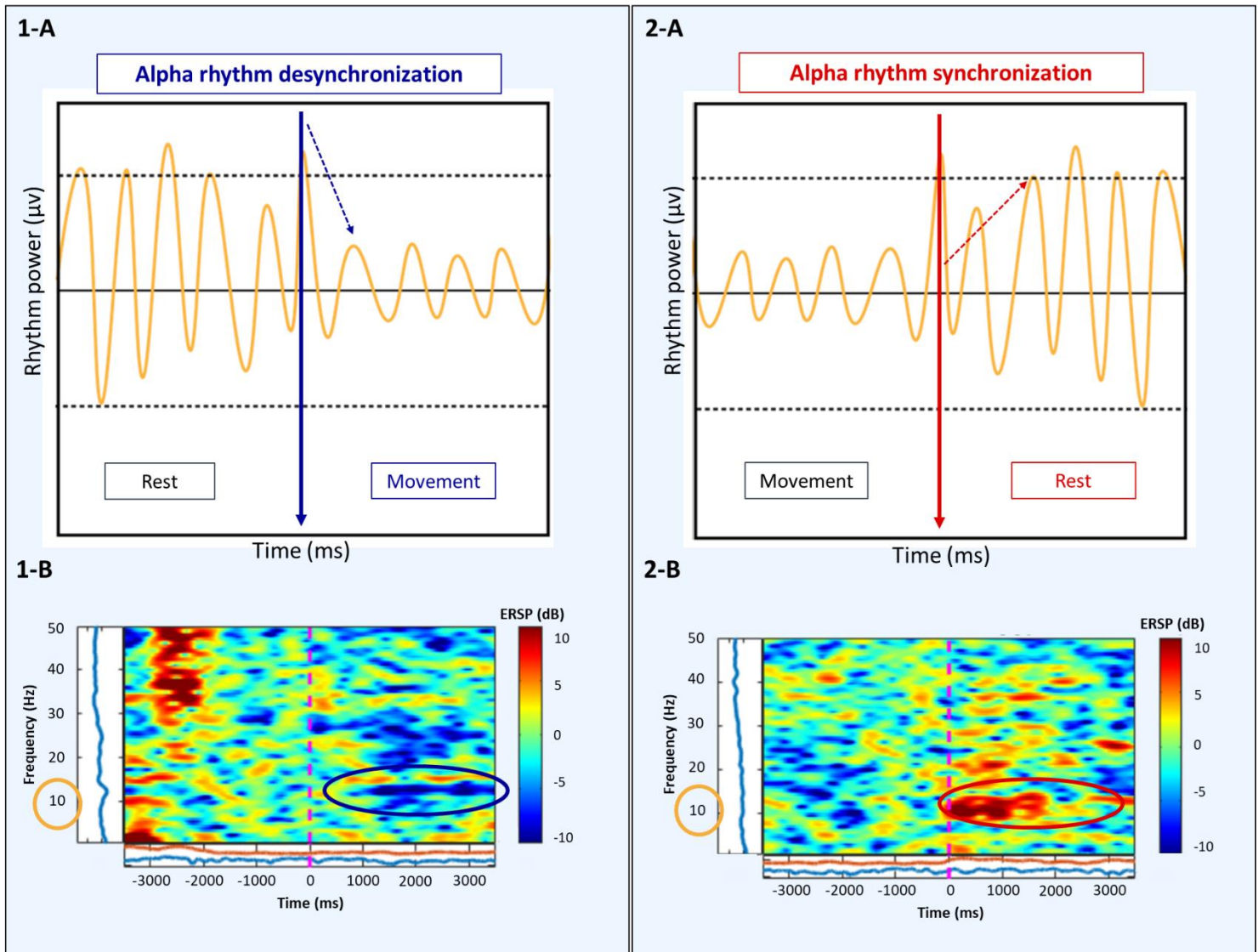


Figure 9 - Illustration of event-related spectrum perturbation.

1. Event-related desynchronization of the alpha-band rhythm (8-13 Hz), A/ Representation of the power decrease following the beginning of a movement, and B/ Time-frequency representation of the rhythm power. 2. Event-related synchronization of the alpha-band rhythm (8-13 Hz), A/ Representation of the power increase following the beginning of a rest period, and B/ Time-frequency representation of the rhythm power. For the ERSP measure, low and high mean dB values are relative to baseline, at each time in the epoch.

Modification of the rhythms' activity seems to play a role in the motor control of movement (Pfurtscheller & Lopes da Silva, 1999a). Indeed, the frequency of brain oscillations depends on the number of synchronously activated neurons and with an increasing number, the frequency becomes in general slower (Singer, 1993). This method to evaluate electrical activity changes related to an internal or external stimuli was renamed event-related spectrum

perturbation (ERSP) to include both ERD and ERS. It is a generalisation of the ERD and measure the mean dynamic changes in amplitude of the different frequencies' bands spectrum as a response to an experimental event (Makeig & Inlow, 1993). Event-related power changes in the neural oscillatory activities contained in EEG signals have been used to decode the movement (Nakayashiki et al., 2014). Unilateral voluntary movement is accompanied by ERD changes in the alpha and beta bands over the contralateral sensorimotor areas (Pfurtscheller & Lopes da Silva, 1999a). Looking to the power modification recorded by ERSP, the oscillations over the SM1 will be characterized by a power decrease during movement execution (ERD) while the resting period is characterized by a power increase (ERS), respectively traducing an activated and deactivated cortical network (Pfurtscheller & Lopes da Silva, 1999b).

3.2.4. fNIRS-EEG association

If fNIRS - EEG methods are providing good spatio-temporal information about functional brain activity, maybe, used together, they could provide a full picture of the NVC (Yeung & Chu, 2022). As explaining before (see sections 3.2.1 and 3.2.2. for details about the NVC) there is a link between electrical activity and cerebral blood flow that supplied glucose via the NVC phenomenon (Girouard & Iadecola, 2006). The changes of the neurovascular and hemodynamic responses to neural activity can be captured temporally using fNIRS (Siesler et al., 2008).

If we have seen that the recorded fNIRS and EEG signals were dependant and related to each other, what can we clearly expect from the use of both neuroimaging methods together? In the literature, the use of combined fNIRS and EEG appears promising for the investigation of functional task-related brain activity. From a methodological point of view, EEG has lower spatial resolution and higher temporal resolution and fNIRS offers better spatial resolution but a poorer temporal resolution (Parasuraman & Caggiano, 2005). Thus, they can overcome each other weaknesses. For the EEG, the poorer spatial resolution could lead to difficulties to differentiate the deactivation / activation of SM1 and pre-motor cortex (NirKKo et al., 2001). With a high temporal resolution, EEG can detect electrophysiological events that span different frequency band and can occur simultaneously or in succession. For the fNIRS, the lower temporal resolution is not allowing such differentiation of electrophysiological signatures with for instance no differentiation between inhibitory and excitatory synaptic activity (Zich et al., 2017). Reversely, the EEG is recording responses of more widespread areas that could lead to spatial differentiation difficulties (NirKKo et al., 2001). Additionally, EEG and fNIRS signals are associated with the neuronal electrical activity and metabolic responses, respectively, providing

a built-in validation for identified brain activity. Measurements obtained from each of these two neuroimaging modalities thereby provide complementary information related to functional activity of the brain. Finally, the integration of these two methods has been presenting a good potential in literature for providing better spatio-temporal functional monitoring of brain hemodynamic and electrical activity in several healthy and pathological population for variety of tasks (for reviews see Li et al., 2022 and Yeung and Chu, 2022).

3.3. Chapter 3 key-points

EVALUATION OF BRAIN AND UL FUNCTION

- Kinematics assessments are providing valid parameters to evaluate the UL function
 - Combining two neuroimaging methods allow for a good spatio-temporal can be used to evaluate the related brain activity
 - EEG – recording of brain electrical activity
 - fNIRS – recording of hemodynamic and metabolic response
- AIM = use adapted evaluation of kinematics and brain activity of UL movement
 - What do we know about aging and stroke effects on task-related brain activity?

Panel 4

Chapter 4: Task-related brain activity

So far, in this theoretical background, we illustrated the importance of the UL function's maintenance (in healthy aging population) and recovery (in stroke population) to maintain and/or improve daily life quality by allowing a maximum of everyday tasks (i.e., getting dressed, reaching objects, eating, cleaning, ...).

Comparing brain activation data from poststroke patients with healthy subjects could have interests in patient management as it could allow a better understanding of brain and kinematics evolution through pathology and rehabilitation. At the beginning of the previous chapter, we presented several methods to evaluate the relationship between functional movement using kinematics and the related brain activity using functional neuroimaging. In this chapter we will present the brain activity changes for specific motor tasks, going through healthy young adults, healthy old adults, and stroke patients.

Finally, as full mobility of the UL is necessary in everyday life activities, it seems relevant to use standardized upper limb movement tasks close from daily tasks. So, in the last part of this chapter we will look through the variety of functional tasks that could be pertinent for questioning the UL function and its brain-related activity.

4.1. Task-related brain activity in healthy people

Before understanding what is going on at the brain and kinematics level during any kind of movement with aging, we have to quickly look to task-related cortical activity in young and healthy human brain. The voluntary commands are controlled at the level of the cortex. If you want to realize a functional task, sensitive information about the instructions, the environment, etc, are going to go up to the cortex, and after being integrated, movement is going to be initiated and produced at the end. We are, in the context of the task execution, interesting in how the sensorimotor areas of the brain are going to 'initiate' a movement.

First, we have to look at the central nervous system regions implicated into UL movement. Somatotopic maps with different degrees of intra- and interlimb separation were identified in the primary motor cortex (M1; Lotze et al., 2000), primary sensory cortex (SM1; (Bushara et al., 2001; Fink et al., 1997; Hlušík et al., 2001), supplementary motor area (SMA; Fink et al., 1997), and cerebellum (Bushara et al., 2001; Grodd et al., 2001; Rijntjes et al., 1999).

As presented in chapters 1 and 2, a clear focus of this thesis is done on UL functional movement as it could have a clear impact on people daily lives. In this context a recent study has looked to cortical and subcortical areas involved in reaching movements, and more specially in their regulation (accuracy, speed; Shirinbayan et al., 2019). They found, using fMRI, relevant activation in the premotor cortex (PMC), M1, SM1, SMA and in sub-cortical areas (i.e., putamen and thalamus). Nevertheless, in this study, the reaching movement was only involving a wrist and elbow movement, thus, a bit far from a full arm proximal reaching that could be used in daily life. If we talk about an asymmetric movement, implicating only one unilateral UL, we have to talk also about brain asymmetry patterns. The laterality has been observed in humans at the level of the structure, function, and behaviour. More especially, the lateralization of the SM1 during UL movement have received lots of interest. An asymmetry has been generally identified between both hemisphere during unilateral movement in favour of a contralateral activity (Ehrsson et al., 2000; Kawashima et al., 1998; Matsunami & Hamada, 1980; Tanji et al., 1988). And some studies have shown that this asymmetry could be reduce when the task's complexity increase as the recruiting if brain areas is added to the already activated areas of simple tasks (Hummel et al., 2003; Kawashima et al., 1998; Sadato et al., 1997; Verstynen et al., 2005). Few studies have investigated the brain-related activation of UL movements involving full arm joints (i.e., wrist, elbow, shoulder). For such unilateral movements, it has been shown by using fNIRS that the contralateral hemisphere is mainly activated (Nishiyori et al., 2016), a more bilateral activation pattern can be observed as compared to distal UL movements (Nirkko et al., 2001).

4.2. Task-related brain activity: healthy aging and compensations models

We earlier presented the physiological and functional aging alteration. To go against the age-related brain modification, neuroplasticity phenomena are occurring. With this brain ability to reorganize itself, it is possible to compensate for the harmful effects of aging. In healthy people, age-related physiological changes alter the neural circuitry at the structural level, especially in the SM1 (Sawaki et al., 2003), as well as the cortico-striatal and the cortico-cerebellar networks (Doyon & Benali, 2005), and at the functional level with regard to neuronal plasticity (Burke & Barnes, 2006). Several models have emerged in the literature to explain these modified brain reorganisation patterns regularly observed in healthy aging during both cognitive and dual-locomotor tasks.

4.2.1. HAROLD model

One of the first exploration on aging effect on the brain-related activity of specific function had been done on cognitive tasks by recording the prefrontal cortex (PFC) activity. At the end of the 20th century, several neuroimaging studies have highlighted that the PFC activity tends to be less asymmetric in older than in younger and two hypotheses have been proposed to explain these modifications: i) an age-related difficulty in recruiting specialized neural mechanisms (de-differentiation hypothesis, Li & Lindenberger, 1999); or a modification to counteract age-related neurocognitive decline (compensation hypothesis, Cabeza, 2002).

To understand the de-differentiation hypothesis, we have to first mention that according to Li and Lindenberger (1999), the decline in the dopaminergic production would degrade neuronal transmission leading to a weakening of the specificity of brain regions and a recruitment of non-specificity regions for a given process. This would lead to de-differentiation phenomena, meaning the elderly would have more bilateral brain activation where younger have lateralised and region-specific ones depending on the task. Few decades ago, this de-differentiation modification in the elderly has been showed on a memory task (Madden et al., 1999; figure 10). The authors observed in older adults that both frontal hemispheres were activated when only the left one was activated for the younger subjects. And those modifications were happening both during planification and movement. More studies have found this de-differentiated brain pattern in several cognitive tasks (Angel & Isingrini, 2015; Cabeza, 2002). This reduced laterality would be the product of a difficulty for older to activate the specialized brain regions. It would be the consequence of structural alterations, and the de-differentiation will be explained by the fact that the same cognitive process is subtended by a more bilateral cerebral activity in older.

The second hypothesis explanation to this lack of de-differentiation has been proposed by Cabeza et al. (2002). The authors defend the idea of compensatory processes where the physiological degradation is a slow process that allow to the brain to adapt progressively. They proposed a model of a reduced asymmetry with aging (HAROLD, Hemispheric Asymmetry Reduction in Older Adults) who suggests that the bi-hemispheric recruitment aims to compensate the neurocognitive decline (Cabeza, 2002; Cabeza et al., 1997). This hypothesis to the hemispheric reduction was supported by studies that showed that this bi-hemispheric activity was associated to an increase in cognitive performance in older people in comparison to older with unilateral brain activity (Reuter-Lorenz et al., 2000; Stebbins et al., 2002). To sum up, it means that to compensate the degradation of performance supported by the neuronal decline, older people will recruit supplementary cognitive resources in the opposite hemisphere. It could thus

be attributed to a change in the cognitive recruitment strategy to reach the goal: succeeding the task.

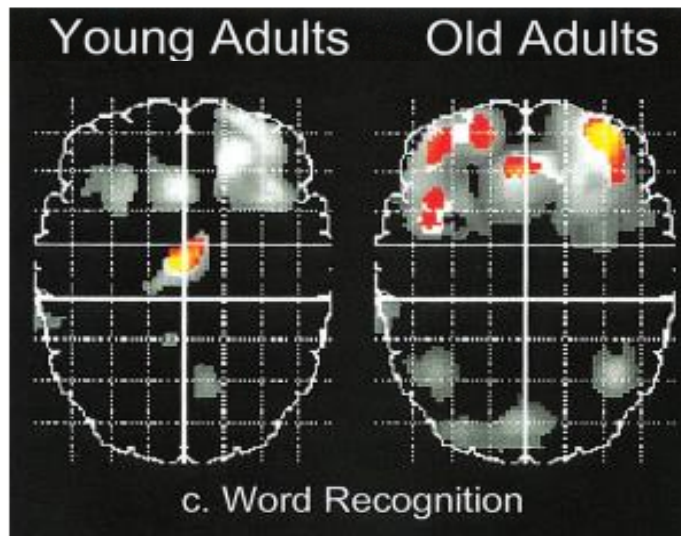


Figure 10 - Asymmetry modification with aging illustrated in a word's recognition task.
Results from Maden et al. (1999)

4.2.2. CRUNCH model

To complete the HAROLD model, another more generic model has been proposed by Reuter-Lorenz and Cappell (2008), the hypothesis of the compensation use of neural circuits (Compensation-Related Utilization of Neural Circuits Hypothesis, CRUNCH). This model suggests that additional neural resources are recruited in elderly to attempt compensation when faced with elevated task requirements due to reduced neural efficiency. It assumes that the level of cerebral activity in elderly is dependent on the task demand and difficulty. And, for a same task, the older will recruit cerebral regions that are not recruited in younger, with for example adjacent recruitment around the activated regions, opposite recruitment to the PFC. To come to this model, authors have observed cerebral overactivation (i.e., higher brain activity as for younger), in older adults during cognitive tasks involving memory and executive functions (Cabeza et al., 2004; Langenecker & Nielson, 2003; Morcom et al., 2003).

The figure 11 is presenting how this overactivation is dealing with the task demand (Martins et al., 2015; Reuter-Lorenz & Cappell, 2008). Firstly, older adults are going to recruit supplementary resources but with a limited cognitive resource. There is a threshold above which one no more supplementary recruitment is possible to improve performances. If the task demand is low enough so that the overactivation can help to reach the final performance, this is considerate as an efficient compensation. Reversely, the compensation is judged inefficient if the individual cannot reach the performance even though he recruited supplementary resources. Coupled to preserved performance, such pattern suggests that increased recruitment compensates for decline (Persson et al., 2006). As presented in figure 15, before reaching the cognitive threshold, the supplementary recruitment would allow to reach the same performance as youngsters.

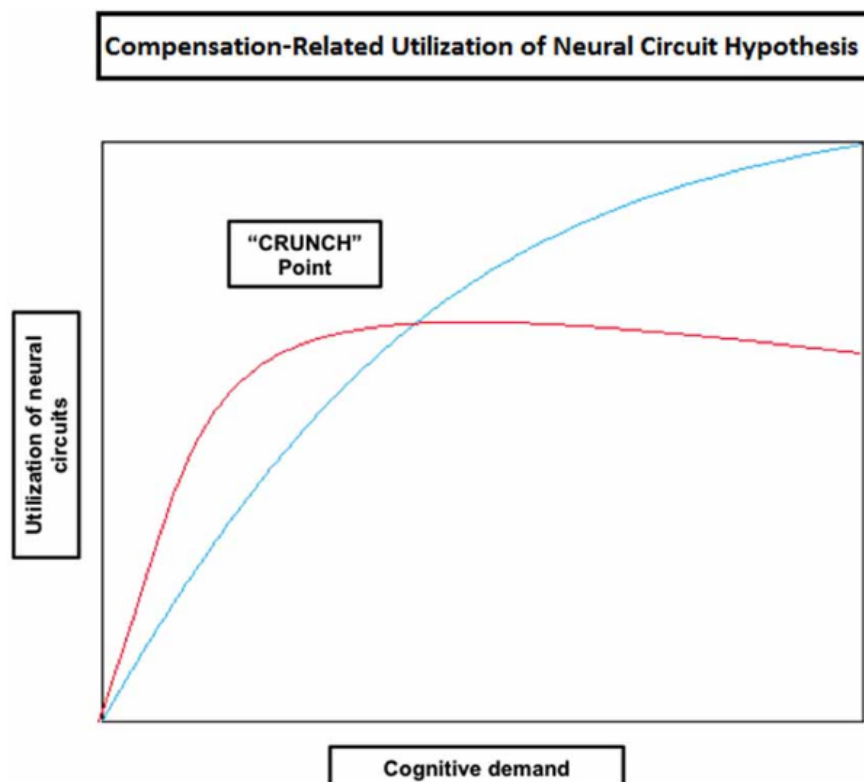


Figure 11 - Illustration of the Compensation-related utilization of Neural Circuits hypothesis (Reuter-Lorenz and Cappell, 2008).

This figure presents the use of neuronal circuits on young adults (blue line) and healthy old adults (red line). Figure from Martins et al. (2015)

4.2.3. STAC model

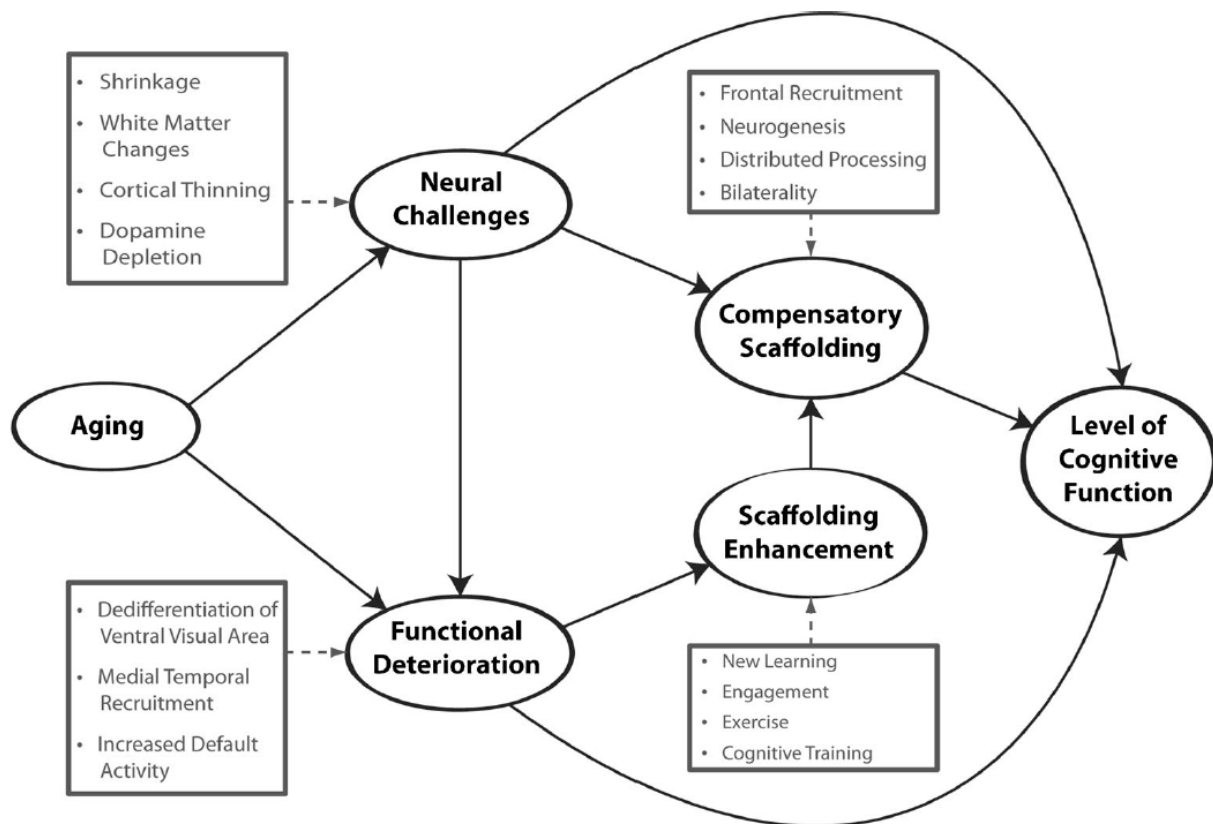


Figure 12 - Illustration of the scaffolding theory of aging and cognition-revised (STAC-r).

STAC posits that behaviour is maintained at a relatively high level with age, despite neural challenges and functional deterioration, due to the continuous engagement of compensatory scaffolding. In the model illustration, from the left to the right, you can see the functional deterioration and neural challenges, the associated compensatory scaffolding and scaffolding enhancement leading to the maintenance of the cognitive function level. Figure from Park and Reuter-Lorenz (2009)

To complete the CRUNCH model and explain the presented overactivation, Park and Reuter-Lorenz (2009) proposed the STAC model (Scaffolding Theory of Aging and Cognition). STAC is a conceptual model whose aim is to better understand the effects of age and cognition from a neurofunctional view. This model is assuming that elderly, to compensate for physiological alteration, will recruit supplementary neural networks who are going to support, like a scaffold, the networks that became less efficient. This will lead to the use of more networks, which is traduced by an overactivation, for older to succeed and maintain a high level of performance on a task. This reorganisation is thus a process answering to a difficulty/ challenge, that is the physiological alteration of neuronal networks with age. Here we have an echo with the neuroplasticity section (2.1). Indeed, this dynamic process of developing supplementary network

is related to this neuroplasticity phenomena. In the context of the STAC model, this compensatory scaffolding is operating to counteract the adverse effects of neural and functional decline with “positive” plasticity that goes with aging. Nevertheless, adverse changes in brain structure occurring with age look like more negative forms of plasticity (Cramer et al., 2011; Greenwood, 2007).

STAC (figure 12) represents the brain as a dynamically adaptive structure that changes in both positive and negative ways with age. Nevertheless, as the neurogenesis is at the origin of the scaffold, the limit of this model will be on the reduced ability of the older brain to recruit new networks (Burke & Barnes, 2006). The need of supplementary resources will grow faster than the ability of neuroplasticity. Thus, at one point, the older person won't be able to compensate for neurophysiological deficits.

4.2.4. Models and motor function

All the models built in the nineties, are mainly relying on cognitive tasks (memory, executive function, language, calculation...). If we go back to the field of functional movement, what the literature is saying about these models and the effect of aging on the control of movement by the brain?

Looking to the aging brain and motor task literature, very few studies have explored this question. For example, in the review of Ishii and colleagues (2017), very few place is given to motor tasks on the aging brain, and the only studies cited have done either cognitive either both motor and cognitive task (i.e., go no go task). In the literature we can also found lower-limb movement brain-related activity in healthy aging (for example recent paper of Hoang et al., 2022), but the literature around UL is brief. If we look to bimanual task, the review of Maes et al. (2017) reported that aging was related to cortical hyper-activity (but also subcortical hypo-activity) during performance of bimanual tasks. Nevertheless, even in bi-manual movement, less than a half of the cited studies have explored movement involving multiple joints of the UL and trunk. Looking now to the unimanual movements, recently, aging brain modification was revealed with hyperactivation of the task-specific motor networks during distal hand-movements in elderly compared to young (Larivière et al., 2019). These authors showed that the maintenance of the grip task performance for the older group was achieved by a greater activation of the involved neural networks. In addition, producing unilateral fine hand motor tasks, such as handgrip or finger tapping tasks, recruits more bi-hemispheric areas for older adults with a greater

activation of SM1 (Daselaar et al., 2003; Van Impe et al., 2011; Michely et al., 2018). With aging, functional movements involving proximal UL joints (shoulder, elbow) are more affected and could present modification in the speed and accuracy components of the movement (Wittenberg et al., 2022). Nevertheless, there is still no information about the effects of healthy aging on changes in brain activation patterns of the sensorimotor network during unilateral multi-joint proximal UL movement tasks seen in daily life.

4.3. Task-related brain activity: pathological aging through stroke

As mentioned in the beginning of this chapter, the movement-related brain activity, the cortical level of a healthy brain is mainly located in the primary and sensory motor cortices (SM1). After a stroke, the motor impairment (see section 1.2.1.) has been related to structural and functional modification in the integrity of descending corticospinal or pyramidal tracts (Lotze et al., 2012; Stinear et al., 2007). These integrity modifications could influence the SM1 activation pattern observed.

4.3.1. Effects of stroke

Functional motor recovery has been attributed to plastic reorganization in the adult human brain (Calautti & Baron, 2003; Ward et al., 2003). Previous research showed that cortical activation and motor recovery after stroke are close processes that depend, among many other factors, on both the time elapsed from the stroke, the initial severity of motor impairments and on stroke location and extent.

Post-stroke brain-related activity can be related somehow to the same hypothesis as in aging. Indeed, this hypothesis is supported by evidence that hemispheric asymmetry reductions may facilitate recovery from brain damage. In early stage of stroke, the activation of the contralesional hemisphere for paretic arm movement could be a result of a loss of inhibition from the lesioned hemisphere on the healthy hemisphere due to the lesion (Calautti & Baron, 2003; Grefkes et al., 2008). An alternative hypothesis is a phenomenon of recruitment of these contralesional sensorimotor areas to face the lack of activation of the lesioned hemisphere (Calautti & Baron, 2003; Rehme et al., 2012). We can here find the same explanation as for the modification of the task-related brain activity of healthy aging: loss of specialization and/or compensation.

As a result of contralateral recruitment, cognitive functions that are strongly lateralized in the healthy brain, may become more bilateral after brain damage and lots of studies have associated a successful functional recovery to bi-hemispheric involvement (Bütefisch et al., 2003; Cramer et al., 1997; Feydy et al., 2002; Pundik et al., 2015). Figure 13 is presenting as example the increase bi-hemispheric recruitment found by Pundik and colleagues (2015). Studies in language found that better recovery of language function in aphasic patients was observed in patients with bilateral activations (Cao et al., 1999; Silvestrini et al., 1993). Reversely, studies have shown that the brain pattern during motor task on well-recovered patients were going toward a progressive “normal lateralized” pattern of the SM1 (Delorme et al., 2019; Feydy et al., 2002; Tombari et al., 2004). This brain pattern is thought to be associated with improvement of motor function (Chollet et al., 1991; Cramer et al., 1997).

The relative activation between the hemispheres ipsilateral to the moving arm and contralateral to the moving arm is commonly referred to as interhemispheric balance. After a stroke, one of the hemispheres is damaged which leads to a disruption in the interhemispheric balance that may require greater use of the healthy hemisphere. To illustrate this concept, we can express the relative contribution of the hemisphere during a motor task with a laterality index (LI), describing the hemispheric dominance (i.e., ipsilateral, contralateral, or bilateral; (Calautti & Baron, 2003). The relevance of fNIRS measures has been shown to assess the contribution of each cerebral hemisphere and thus a proxy of the interhemispheric balance by measuring the lateralization of brain of cerebral activations (Delorme et al., 2019; Derosière et al., 2014). With this notion of modification of the hemispheric balance through stroke rehabilitation, the relationship between functional recovery of the paretic arm and an interhemispheric rebalancing towards the levels observed in healthy subjects has been observed (Delorme et al., 2019).

As presented in previous section, for lateralized motor task in healthy young subjects, the activity is mainly located in the contralateral SM1, and for older it can be already more bilateral depending on the tasks demand and features. In stroke patients, SM1 LI values for the paretic arm are lower and even negative, due to both decreased ipsilesional activity and increased contralesional activity (Favre et al., 2014). For example, neurological impairment following a stroke has been shown to induce greater bilateral SM1 activation compared to healthy aged individuals when performing reaching and hand grip movements (Lim & Eng, 2019). This hemispheric balance is considered as one potential marker of recovery in stroke functional

neuroimaging studies (Cramer et al., 1997). Over time, we could observe a shift toward the ipsilesional hemisphere (Favre et al., 2014; Marshall et al., 2000; Michielsen et al., 2011).

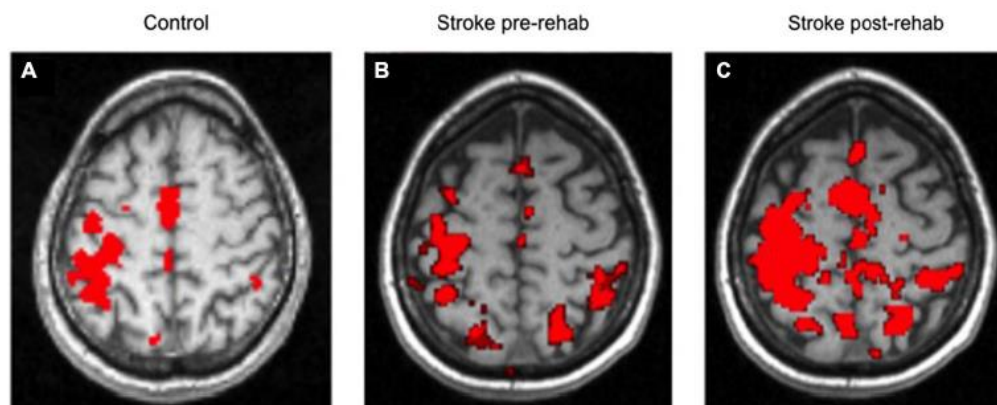


Figure 13 - Example of post-stroke bi-hemispheric recruitment

In this example, we can see an increase of brain activation at post-treatment. Figure from Pundik et al. (2015)

To our knowledge there are few studies about the functional UL proximal movement and stroke using functional neuroimaging. Recently, a study by Lim and Eng (2019) have looked to the bi-hemispheric brain activity in motor cortices during a forward cube grasping task (i.e., Box and Blocks test). The authors found a greater sensorimotor activation in the ipsilesional hemisphere for the stroke compared with healthy during reaching and grasping accompanied with poorer performances. Moreover, the authors found a correlation between gripping performance and sensorimotor brain activation; the better performance in the stroke individuals was related to a greater brain activity. Nevertheless, authors did not record any kinematics data in their study, and this acquisition could give interesting information's about how the characteristics of the movement are evolving in stroke in relationship to the brain reorganizations.

4.3.2. Effects of rehabilitation

The movement-related brain activity is evolving with stroke UL rehabilitation, but can we use it as a marker of recovery?

It was recently suggested that post-stroke brain was able to return to the state of healthy brain organisation during subacute recovery (subacute stage in Delorme et al., 2019). In this study it was suggested that SM1 activity was significantly correlated with concomitant changes in functional clinical assessment (motor recovery tests assessed by Fugl-Meyer score). This relationship between ipsilesional increase activity and UL recovery has been also shown in other neuroimaging studies (Calautti et al., 2001; Tombari et al., 2004; Wiest et al., 2014). In another

study looking to hand dexterity, it has been shown that for patients with better hand dexterity level, there were decrease over time in the contralesional motor areas while interhemispheric balance returned to healthy control levels (Wiest et al., 2014). In contrast, patients with poor recovery presented with sustained hypoperfusion in SM1s encompassing the ischemic tissue and cerebral blood flow remained lateralized to the contralesional hemisphere. Whether a link is possible between the functional neuroimaging markers, the kinematics of movement, and the functional recovery, using neuroimaging methods could be relevant to guide any therapeutic interventions aiming to promote neuroplasticity. Most of the time, studies looking to post-stroke patients showed an ipsilesional dominant activation pattern in patients with good or complete motor functional recovery but not in poorly recovered patients (Chollet et al., 1991; Cramer et al., 1997; Ward et al., 2003).

4.4. Which tasks to evaluate UL function?

As we often repeat it in the aforementioned sections, to maintain the autonomy of patients of older, the functional movement is a key point. Understanding the kinematics and related- brain activity level is an important possibility to identify markers of good recovery for example. Nevertheless, there is a lack in literature in the kind of tasks and population observed.

In most longitudinal post stroke functional neuroimaging studies, the authors used either a finger-tapping task (Chollet et al., 1991; Cramer et al., 1997) or repeated flexion-extension of a segment of the upper limb (Feydy et al., 2002; Van Dokkum et al., 2017) or hand grasping (Grefkes et al., 2008; Rehme et al., 2012; Takeda et al., 2007). However, the authors did not give information on the use of the paretic arm and/or the use of the trunk during the execution of this task which could be interesting in the context of stroke rehabilitation.

In the majority of studies that have exploited functional neuroimaging in post-stroke subjects, the tasks and motor actions used were quite different from the isotonic muscle contractions encountered in daily life. Indeed, to accomplish daily life tasks, the proximal movement matter a lot, for example, to get dressed, to reach objects, in brief, to interact with the environment. Moreover, in the context of stroke, proximal movements are allowing an evaluation of the patients early in the recovery paths. Indeed, since functional recovery is proximo-distal, patients are firstly going to recover at the level of the proximal movement. The distal motricity is going to be evolved latter and will only concern patients with a good recover, thus, less patients. Thus, interesting in the functional movement could help to screen more patients.

It would therefore appear necessary to use a more functional task with motor patterns similar to tasks used in daily life, such as grasping, picking up a glass. Finally, information is missing about the effects of rehabilitation on the task-related brain activity and kinematics in chronic stage patients. Thus, developing UL functional tasks, evolving a complete use of the arm joints (proximal movement) and allowing the measure of trunk compensation, appear necessary.

4.5. Chapter 4 key-points

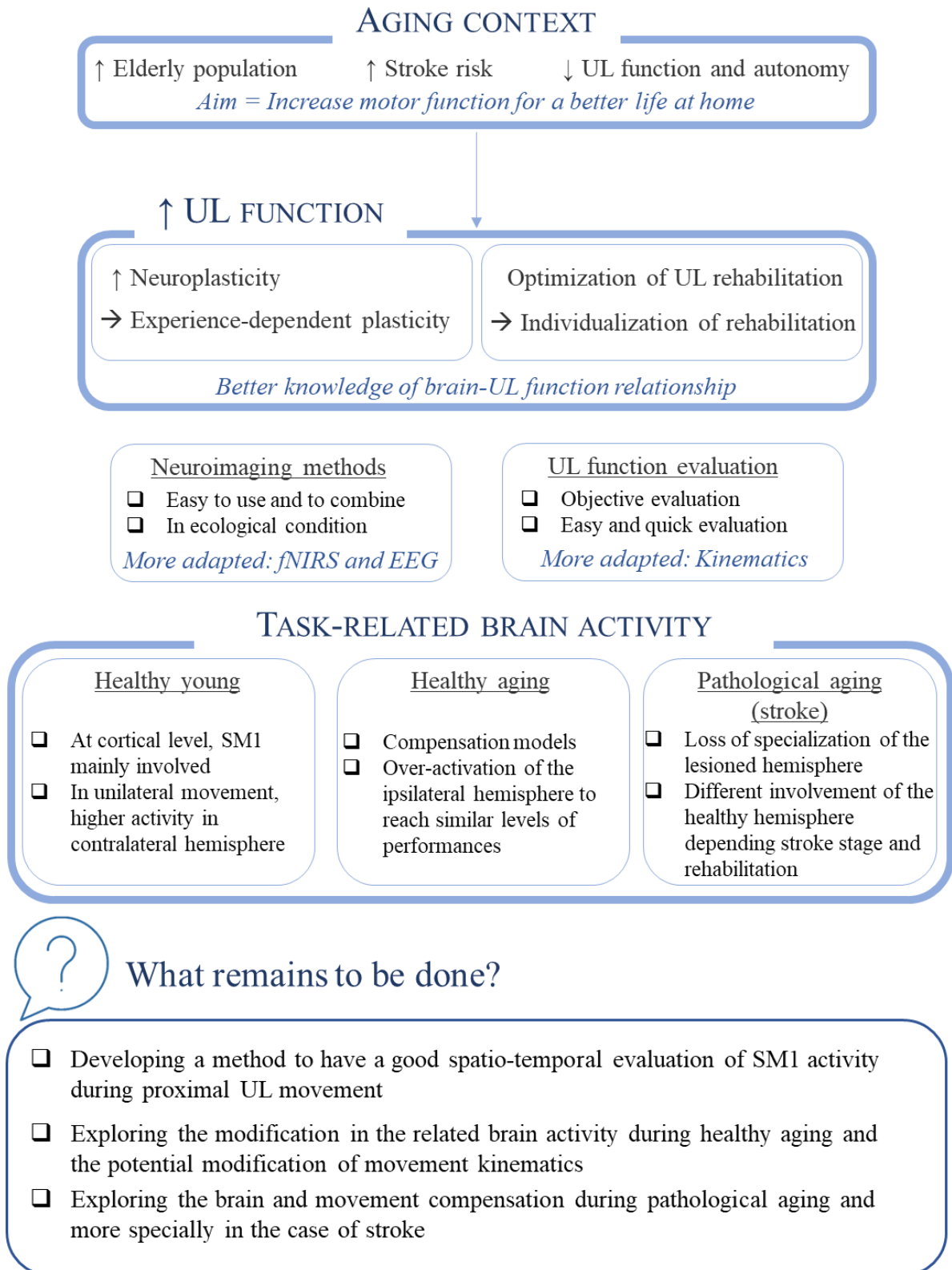
TASK-RELATED BRAIN ACTIVITY

- In healthy young adults
 - Contralateral SM1 mainly involved during unilateral movements
 - In healthy old adults
 - Compensation and lower asymmetry
 - In stroke adults
 - Loss of differentiation and compensation of healthy hemisphere
 - Lack of tasks evaluating proximal movement related brain activity
- There is a necessity in developing methods to assess proximal movement related brain activity

Panel 5

Chapter 5: Literature summary and thesis objectives

5.1. Literature summary



5.2. Thesis problematic and objectives

With aging population, the number of stroke patients is increasing, and it is a major society issue. In this context, the aim is to preserve as much as possible the motor functional abilities of the elderly and/or patients. Thus, focusing on the functional movement and more specially on the upper limb one is important as it is including in most of the daily life activities (brushing teeth, drinking, cooking, using a computer ...).

Post-stroke brain activations and their evolution through rehabilitation is a subject of major interest for a while. Two non-invasive neuroimaging methods allow for recording the task-related brain activity for bedside use or in field monitoring: functional near-infrared spectroscopy (fNIRS) and electroencephalography (EEG), respectively based on hemodynamic response and electrical activity of brain regions. Coupling both methods could lead to a better spatiotemporal cortical activity analysis related to UL tasks to unveil underlying UL recovery mechanisms. To study the brain-movement links in Stroke patients, it is necessary to study them first in healthy subjects, then in aged subjects, and finally in patients, in order to define in the anomalies observed what is due to physiological aging and what is due to the effect of the stroke.

This thesis aimed to determine the effects of healthy aging and stroke on the brain activity and kinematics of upper limb proximal movement. This work was built on three main objectives.

The first objective was to develop a complete methodology to assess the UL function with simultaneous task-related brain activity and kinematics measurements. For this purpose, we setup two functional UL task and an innovative methodology to record simultaneously functional SM1 activity and movement kinematics. This setup development was done inside a clinical trial aiming to explore these issues during a rehabilitation program combining VRT and HD-tDCS and resulted in a methodological paper.

The second objective was to delineate the effects of healthy aging on the related brain activity of UL functional tasks. Here we collected the EEG and fNIRS responses over SM1 during unilateral proximal UL movements. For this purpose, a first experimental study was run, and two groups of healthy people were included: one young (18-35 years old) and one older (60-90 years old) groups. The experimental setup was identical on all experimental parts of this project. Subjects participated in a testing session where they performed two functional tasks while their SM1 activity were recorded. This first study was aiming to confirm the age-related modification in the neural networks on specific functional task chosen for their interest in stroke rehabilitation.

The third objective was to evaluate the effects of pathological aging on the task-related brain activity. For this purpose, we compared the data of the first experimental study to a group of chronic stroke patients at the beginning of their rehabilitation program. The idea here was to highlight the effects of brain pathology with regards to some reference/standards of kinematics and brain activity patterns observed in healthy adult controls.

Based on the findings of the previous studies, a better understanding and monitoring of the expected and recorded task-related brain activity in healthy and pathological aging could allow to improve the individualisation of the patients care, using more adapted rehabilitation depending on the patients' state at both the brain and movement levels.

3

PART III - PERSONAL CONTRIBUTION

Chapter 6: Methodology

6.1. Context and objectives

This thesis aimed to evaluate age-related and stroke-related modifications on the kinematics and brain activity during functional motor tasks of the UL. Thus, the methodology used around the functional movement and brain activity evaluation has been an important part of this first personal contribution. Indeed, part of this thesis is taking part of a big clinical trial (ClinicalTrials.gov Identifier: [NCT04291573](https://clinicaltrials.gov/ct2/show/study/NCT04291573)) aiming to deal with the effects of VRT and HD-tDCS contribution on the UL functional recovery. Inside this project, we wanted to explore the effect of this specific rehabilitation methods on the brain-movement activity. Nevertheless, due to sanitary context (COVID19-pandemic), the clinical project started later and is still not finished. Thus, without these rehabilitation data, we decided to target a research axis of healthy aging and one of stroke aging. To answer to the first objective of this thesis, we developed, inside the aforementioned clinical project, a methodology to explore the function UL task-related brain activity and kinematics. The clinical part as well as all the methodological issues have been published in a dedicated peer-review journal (Study protocol in *Trials*) providing lots of details about the methodology used. Below, sections 6.3. and 6.4. provide more details about the methodology to measure concurrently movement kinematics and EEG and fNIRS signals regarding the two functional tasks presented in figure 5 of the first article (Muller et al., 2021).

6.2. Study protocol


ARTICLE 1: Muller C.O., Muthalib M., Mottet D., Perrey S., Delorme M., Duflos C., Froger J., Xu B., Faity G., Pla S., Jean P., Laffont I., Bakhti K. (2021). **Recovering arm function in chronic stroke patients using combined anodal HD-tDCS and virtual reality therapy (ReArm): a study protocol for a randomized controlled trial.** *TRIALS*, 22:147. <https://doi.org/10.1186/s13063-021-05689-5>.

STUDY PROTOCOL

Open Access

Recovering arm function in chronic stroke patients using combined anodal HD-tDCS and virtual reality therapy (ReArm): a study protocol for a randomized controlled trial



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Abstract

Background: After a stroke, 80% of the chronic patients have difficulties to use their paretic upper limb (UL) in activities of daily life (ADL) even after rehabilitation. Virtual reality therapy (VRT) and anodal transcranial direct current stimulation (tDCS) are two innovative methods that have shown independently to positively impact functional recovery of the paretic UL when combined with conventional therapy. The objective of the project will be to evaluate the impact of adding anodal high-definition (HD)-tDCS during an intensive 3-week UL VRT and conventional therapy program on paretic UL function in chronic stroke.

Methods: The ReArm project is a quadruple-blinded, randomized, sham-controlled, bi-centre, two-arm parallel, and interventional study design. Fifty-eight chronic (> 3 months) stroke patients will be recruited from the Montpellier and Nîmes University Hospitals. Patients will follow a standard 3-week in-patient rehabilitation program, which includes 13 days of VRT (Armeo Spring, 1 × 30 min session/day) and conventional therapy (3 × 30 min sessions/day). Twenty-nine patients will receive real stimulation (4x1 anodal HD-tDCS montage, 2 mA, 20 min) to the ipsilesional primary motor cortex during the VRT session and the other 29 patients will receive active sham stimulation (2 mA, 30 s). All outcome measures will be assessed at baseline, at the end of rehabilitation and again 3 months later. The primary outcome measure will be the wolf motor function test. Secondary outcomes will include measures of UL function (Box and Block Test), impairment (Fugl Meyer Upper Extremity), compensation (Proximal Arm Non-Use), ADL (Actimetry, Barthel Index). Other/exploratory outcomes will include pain, fatigue, effort and performance, kinematics, and motor cortical region activation during functional motor tasks.

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Discussion: This will be the first trial to determine the impact of adding HD-tDCS during UL VRT and conventional therapy in chronic stroke patients. We hypothesize that improvements in UL function will be greater and longer-lasting with real stimulation than in those receiving sham.

Trial registration: The ReArm project was approved by The French Research Ethics Committee, (Comité de Protection des Personnes-CPP SUD-EST II, N°ID-RCB: 2019-A00506-51, <http://www.cppsudest2.fr/>). The ReArm project was registered on ClinicalTrials.gov (NCT04291573, 2nd March 2020).

Keywords: HD-tDCS, Upper limb function, Virtual reality therapy, Stroke, Rehabilitation, Laterality index, Monitoring, Upper limb use, Cortical activation

Background

With a very high prevalence, stroke is the second cause of death and the first cause of acquired disability in adults in well-developed countries. Stroke frequently leads to sensory-motor and functional physical limitations [32]. It is also responsible of 2 to 4% of total expenses in health care with a need of developing new re-educative treatments [32]. Hemiparesis is one of the most common disabilities caused by stroke. Poor recovery of the paretic UL function affects more than 80% of stroke survivors [26] and is mostly persistent 3 months post-stroke, in the late sub-acute and chronic stages, even after intensive rehabilitation [54]. Although, repetitive motor training appears to be efficient for improving paretic UL function [73], there is no standardized protocol for the rehabilitation of the paretic UL after stroke [60]. The lack of recovery often results in non-use of the paretic UL [68], leading to reorganization of brain functional networks [48] and finally restricting use dependent functional recovery [50].

Stroke leads to spontaneous reorganization of the central nervous system corresponding to neural plasticity [34]. Spontaneous recovery and regeneration mechanisms of brain reorganization are triggered soon after a brain lesion. Over time, from late sub-acute stage to chronic stage of stroke, there is less and less spontaneous plasticity and it is more difficult to recover paretic UL function [34]. During the late sub-acute and chronic stages after a stroke, experience-dependent plasticity takes on a greater role for functional recovery of the paretic UL [37]. Some aspects of the rehabilitation program (e.g., intensity and volume of practice, variety, specificity, motivation, and biofeedback) can modulate this experience-dependent plasticity [38, 65]. In this context, virtual reality therapy (VRT) that combines rehabilitation exercises with gaming elements appears to be a well-suited intervention in promoting functional recovery of the paretic UL [45].

VRT can be defined as the use of a brain-computer interaction method [70] for providing patients multimodal sensory and motor stimuli with the help of immersive environment workspaces. Herein, VRT allows a

simulated practice of functional motor tasks with more repetitions than in conventional therapy used in post-stroke rehabilitation [19, 40, 70]. Furthermore, VRT can limit fatigue and loss of enthusiasm and improve patient cooperation and engagement, which can positively influence recovery of the paretic UL [42, 43, 67]. As such, biofeedback provided to the patient during VRT was shown to improve the activation of the lesioned hemisphere, fostering a better relearning of motor tasks [33]. A recent Cochrane review [45] indicated that VRT is equally effective in improving paretic UL function compared to conventional therapy (low-quality evidence); however, there was some evidence that VRT resulted in a slightly better ability to manage ADL such as showering and dressing (moderate-quality evidence). Moreover, when combined with a conventional therapy rehabilitation program post-stroke, VRT more efficiently improves paretic UL function and patient's capability to succeed in ADL [41, 45]. Among the VRT methods available, robot-assisted VRT systems use an exoskeleton providing assistive control of the paretic UL (e.g., through counter-gravity springs, such as Armeo system) and thus allows longer training sessions with reduced fatigue [49]. Accordingly, robot-assisted VRT has been shown to achieve greater and long-lasting improvements in paretic UL function in comparison to conventional therapy alone [69].

Enhancing recovery of paretic UL function after stroke can also result from non-invasive brain stimulation (NIBS) through modulation of motor cortical excitability. NIBS has the ability to modulate neural excitability and generate new neuronal associations inducing in turn brain plasticity [62]. Among NIBS techniques, transcranial direct current stimulation (tDCS), which applies low currents around 1–2 mA during 10 to 30 min for single or multiple sessions [10, 15] is a promising clinical potential that can be easily added onto an UL rehabilitation protocol. Moreover, its active sham mode enabling randomized clinical trials allows to apply brief stimulation (10–90 s) while the patient is receiving a rehabilitation treatment that provides the same scalp sensations as a real stimulation session [61, 63]. By increasing

ipsilesional motor cortical excitability and promoting neuroplasticity, anodal tDCS added to motor task training has been shown to improve functional recovery of the paretic UL after a stroke [1, 23–25, 70]. Allman et al. [1] reported long-term (3 months) improvements in functional paretic UL clinical assessments (Wolf Motor Function Test (WMFT), Action Research Arm Test (ARAT)) in chronic stroke patients (> 6 months) with ipsilesional anodal tDCS added to daily hand and arm motor rehabilitation training over 2 weeks (9 × 1-h sessions) compared to sham stimulation. This study also showed an increased movement related cortical activation and grey matter volume in ipsilesional motor cortical regions for patients in the stimulation group compared to sham. Figlewski et al. [23] applied anodal tDCS to the ipsilesional motor cortex during constraint-induced therapy in chronic stage stroke patients (3–36 months) over 2 weeks (9 × 6-h sessions) and found greater improvements in paretic UL function (WMFT) when compared with constraint-induced therapy alone. A recent Cochrane review [22] indicated the effectiveness of tDCS versus sham for improving ADL outcomes after stroke (low to moderate quality evidence). Altogether, these studies provide clinical support that adding anodal tDCS to a rehabilitation program may bolster more the recovery of paretic UL function and ADL in chronic stroke patients. Indeed, anodal tDCS might facilitate activity-dependent plasticity within the neural networks recruited already within a rehabilitation treatment, thereby contributing to greater and sustainable clinical gains [1, 11, 23].

The two aforementioned adjunct stroke rehabilitation methods (VRT and anodal tDCS), used separately as a complement to conventional rehabilitation are expected to improve and maintain recovery of the paretic UL by positively impacting neuroplasticity. Thus, to enhance the effect of conventional therapy, adding anodal tDCS during VRT could be more efficient than when VRT is used alone [66, 70]. However, there is a paucity of studies that have evaluated the effectiveness of this VRT and anodal tDCS combination in post-stroke rehabilitation. Triccas et al. [71] investigated the effects of adding anodal tDCS (ipsilesional motor cortex, 1 mA, 20 min) to an 8-week robot-assisted VRT (Armeo spring exoskeleton) rehabilitation program (18 × 1-h sessions) for early sub-acute (2–3 months) and chronic (9–61 months) stroke patients. Although the addition of anodal tDCS to VRT was well tolerated, there were no added clinical benefits (Fugl-Meyer Assessment, ARAT, Motor Activity Log (MAL), Stroke Impact Scale (SIS)) of such a combination. The authors considered that the low number of sessions of VRT per week (2–3 sessions) and the small/heterogeneous group of patients per group ($n = 11$) might have reduced the chances of detecting a clinical

difference between groups. Moreover, the standard anodal tDCS montage used could prevent significant changes of excitability within the target brain regions. Improving the focality of tDCS effects over sensorimotor regions with anodal high definition (HD)-tDCS was found to induce a greater increase in cortical excitability [39] and haemodynamic activity [55] comparatively to conventional tDCS montage in healthy subjects and thus, might induce a greater neuroplasticity stimulus. Chhatbar et al. [17] reported from a meta-analysis of tDCS UL motor recovery studies a dose–response relationship with electrode size and current density, such that a higher current density or smaller electrode size being associated with greater efficacy on paretic UL motor recovery (Fugl Meyer Upper Extremity (FM-UE)) in chronic stroke. Therefore, it can be expected that applying a more intensive anodal HD-tDCS (2 mA, 20 min) and VRT program (3 weeks, 13 × 30-min sessions) will provide greater clinical benefit [21].

The ReArm project is a randomized-control trial of late subacute and chronic stroke patients (> 3 months) designed to determine the impact of adding anodal HD-tDCS (2 mA, 20 min, ipsilesional motor cortex), compared to sham, during an intensive 3-week UL VRT program (13 × 30-min sessions) supplementing a conventional therapy program (39 × 30-min sessions). The primary objective will be to evaluate the impact of this intervention on paretic UL function 3 months after the end of the rehabilitation. Secondary and exploratory objectives will be to investigate the evolution of the paretic UL use in ADL, performance, kinematics, and movement-related activation of motor cortical regions during functional motor tasks, from the beginning to the end of the 3-week program and after 3 months. We hypothesize that adding anodal HD-tDCS during VRT, as a supplement to conventional therapy rehabilitation program, will result in greater retention of clinical benefits 3 months after the intervention and increased use and functional recovery of the paretic UL.

Methods

Ethics

The study was approved by the National Research Ethical Committee (Comité de Protection des Personnes-CPP SUD-EST II, No. ID-RCB 2019-A00506-51, <http://www.cppsudest2.fr/>) and is registered on <http://www.clinicaltrials.gov> (NCT number, NCT04291573).

Participants

Fifty-eight adult hemiparetic stroke patients will be recruited (see “Sample size” section for details).

Inclusion criteria

Inclusion criteria will be patients (1) aged between 18 and 90 years old, (2) at more than 3 months of a first cerebrovascular accident of any aetiology (haemorrhagic or ischaemic), and (3) with UL motor impairment (FM-UE ≥ 15 [27]).

Exclusion criteria

Exclusion criteria will be patients (1) that fail to give written informed consent, (2) with uncontrolled epilepsy, (3) with pacemaker or any metallic object implanted in the brain, (4) who are pregnant or breastfeeding, (5) that have hemineglect or severe attentional problems (omission of more than 15 bells on the Bell's test [29]), (6) with aphasia of comprehension dysfunction (Boston Diagnostic Aphasia Examination $< 4/5$ [36]), (7) with severe cognitive dysfunction (Mini Mental State Examination-MMSE < 24 [35]), (8) not covered by a French social security scheme, and (9) under guardianship.

Settings and recruitment

Patients will be recruited from in-patient and out-patient clinics at the physical and rehabilitation medicine (PRM) departments of the two university hospitals (CHU): Lapeyronie (Montpellier, France) and Nimes (Grau du Roi, France). Before including patients in the ReArm protocol, the medical physician taking care of the patient will check if the patient fits with the inclusion criteria and does not present any exclusion criteria during a usual clinical outpatient visit. The adherence of patients will be improved by an in-patient rehabilitation stay (patients will sleep at the hospital during training days). The investigators will be available any time to explain to the patient the objective of this project.

Study design

Figure 1 shows a flow diagram of the study design. The ReArm project is a quadruple-blinded, randomized, sham-controlled, bi-centre, two-arm parallel, and interventional study. All patients will undergo 3 weeks of a standard in-patient stroke rehabilitation program (see details in the next section) and will thereafter be followed over a period of 3 months. One group (intervention) will receive 3 weeks rehabilitation consisting of standardized conventional therapy rehabilitation and combined VRT and anodal HD-tDCS. The second group (placebo) will receive standardized conventional therapy rehabilitation and combined VRT and sham HD-tDCS.

Randomization

The Capture System software (Ennov Clinical, module randomization, Paris, France) will be set up by the randomization administrator, from the Innovation and

Research Department of the Hospital, to give a blinding code to each patient. A centralized randomization will be performed using the Capture System software (Ennov Clinical, module randomization, Paris, France). A minimization algorithm will assure the balance of groups regarding PRM centres (CHU Montpellier or Nimes) and stroke severity (FM-UE score lower or higher than 40 [72]); see "Blinding of group and stimulation protocols" section for more details. For each inclusion, another hospital department, the clinical investigation centre, will use the software to allocate the right protocol.

Standard in-patient stroke rehabilitation program

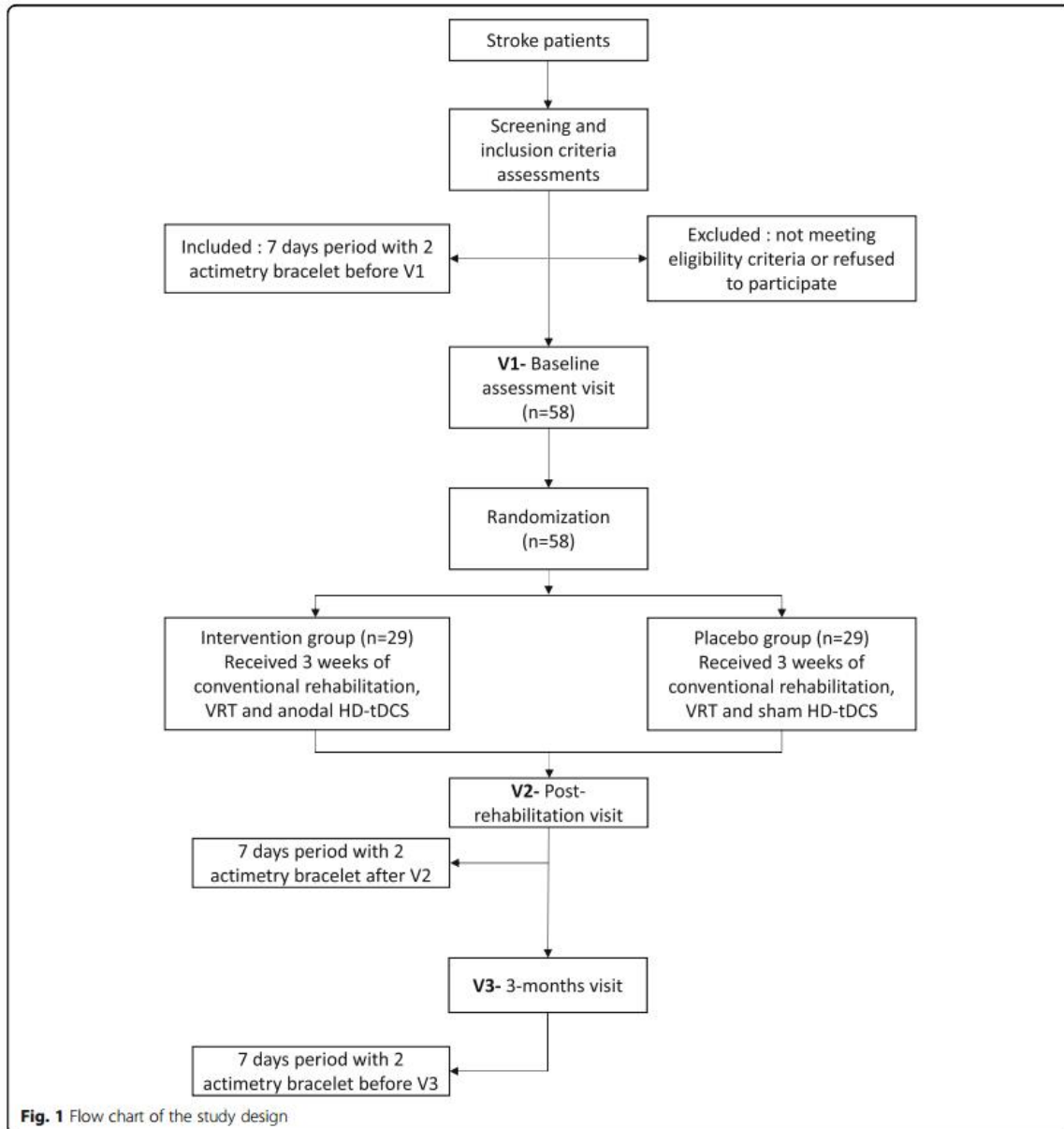
Both the intervention and placebo groups will follow the standard in-patient stroke rehabilitation program usually proposed to stroke hemiparetic patients at the Montpellier and Nimes PRM Departments, which includes both conventional therapy and VRT sessions on each day of a 3-week in-patient stroke rehabilitation program. In both PRM departments, VRT has been, since 2014, included in the standard in-patient stroke rehabilitation program.

Conventional therapy sessions

Conventional therapy includes physiotherapy (1 \times 30 min) and occupational therapy (2 \times 30 min) sessions spaced over the morning and early afternoon each day. Each session is adapted to the fatigability and recovery of each patient. The physiotherapy session focuses mainly on trunk balance, sensorimotor exercises, standing balance and walking workout, and muscular and cardio-respiratory reconditioning to effort. The occupational therapy sessions are oriented towards sitting and standing balance workout, sensorimotor exercises for movement restoration, and may include prehension exercise, and mirror therapy. A daily speech therapy session will be added when required (language troubles).

Virtual reality therapy (VRT) sessions

In addition to the conventional therapy sessions, each day, patients will receive a 30-min VRT session using an UL exoskeleton (ARMEO[®], HOCOMA, Volketswil, Switzerland) providing spring-based anti-gravity support. The ergonomic and adjustable exoskeleton embraces the whole UL, from shoulder to hand and counterbalances the weight of the patient's UL. The Armeo spring VRT system enables hemiparetic patients to achieve more movements in a 3-dimensionnal workspace than they could usually do without anti-gravity support [53, 69]. The Armeo exoskeleton is connected to a computer displaying meaningful functional tasks (e.g., cleaning a window) on a computer screen. Sensors record the active movements and all joint angles during the therapy session.



This semi-immersive VRT provides auditory and visual feedback during and after games training. The virtual environment allows to change the type of games and their difficulty but the main objective of all the games is focused on mobilization of the entire paretic UL with some games also including pro/supination (e.g., flower watering) and grasping with the paretic hand (e.g., egg cracking).

Initially, the patient is comfortably seated on the Armeo system; the display screen is placed 75 cm

from the patient and the centre of screen 20 cm below the eyes (Fig. 2). The parameters of the ARMEO® (e.g., exoskeleton arm and forearm lengths, arm and forearm anti-gravity compensation, auto-grip), will be set for each patient on the first day (V1) and will not be changed for subsequent sessions. To counterbalance the weight of the patient's UL, the upper arm and forearm weight compensation is half for all patients. The UL is straight forward if the patient does not move (rest position).

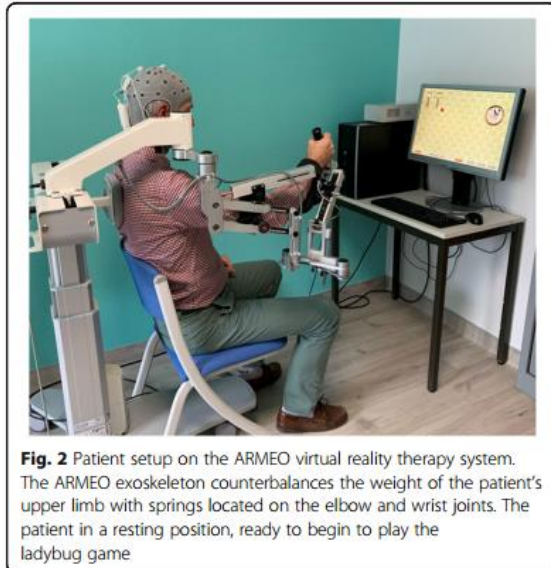


Figure 3 shows 4 examples of the Armeo VRT rehabilitation games. For all patients, each session will start and end with the *Ladybug* game (Fig. 3a), a speed-accuracy test where the patient has to point to the ladybugs (targets) appearing on the screen as fast as possible. The rehabilitation games during the first 20 min of the session will remain identical for all subjects, with the same program order of 9 rehabilitation games (see Table 1). These 9 games enable patients to use any remaining UL motor function (shoulder, elbow, hand) in a 3D workspace. The 9 games include one 3D game (Reveal Panorama), seven 2D games in frontal or horizontal plane (window mopping, egg cracking, fish catching, popping air bubbles, fruit shopping, stove cleaning, reaction time) and one 1D game (snow balls). The next 10 min will include rehabilitation games selected specifically to each patient's preferences and abilities (e.g., pro/supination). The therapeutic plan for the final 10 min of the 30-min session (order and type of exercises) will be decided during the first session by the therapist in charge of the patient (trying games with them). Patients will be asked to provide feedback after the first session concerning the difficulty of the games, their ability to achieve them, and their preferences. This will allow the

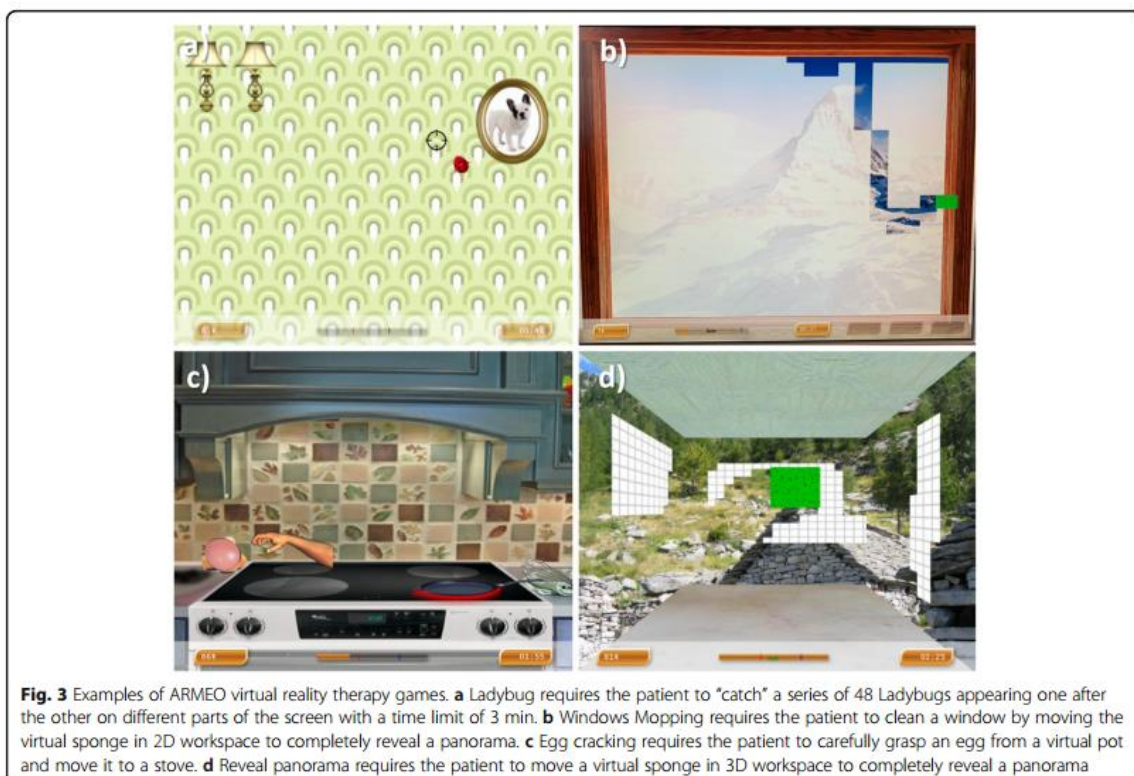


Table 1 List of the ARMEO virtual reality therapy games detailing the upper limb joints, movements, and workspace

Name of the games	Joints				Workspace/plane
	Elbow ext./flex. ^a	Shoulder ext./flex.	Shoulder horiz abd./add. ^b	Hand (grasp)	
Windows mopping	X	X	X	X	2D/frontal
Reveal panorama	X	X	X	X	3D/frontal + horizontal
Egg cracking	X	X	X	X	2D/frontal
Fish catching	X	X	X		2D/frontal
Popping air bubbles	X	X	X	X	2D/frontal
Snow balls	X	X			1D/horizontal
Fruit shopping	X	X	X	X	2D/frontal
Stove cleaning	X	X		X	2D/horizontal
Reaction time	X	X	X		2D/frontal

^aExtension/flexion^bHorizontal abduction/adduction

therapist to choose the games of the last 10 min of the session. Each patient will follow the set rehabilitation games program configured to their ability that will remain identical for all subsequent sessions.

The difficulty of the rehabilitation games will be initially set at the highest level (e.g., smallest size of sponge for the window mopping game, see Fig. 3b) in order to allow improvements in performance over the training sessions. Moreover, if a patient achieves a maximum score of 100% on a game with a time limit, they will be able to further improve their performance reducing the time of the game which will be recorded. Depending on the paretic hand recovery level of the patient, auto-grip will be activated or not. Auto-grip is not activated for patients able to grasp. However auto-grip is activated when the patient just needs to move the UL to the location of the target without requiring a hand grip force to secure the target. The auto-grip will be modified to be off during the rehabilitation program if the hand grip ability of the patient improves. The Armeo software presents online and subsequently records each participant's performance for each rehabilitation game (i.e., time, game performance). The software also records the kinematic movements of the exoskeleton, which will be used for the ladybug end effector trajectory analysis.

Anodal high definition transcranial direct current stimulation (HD-tDCS)

Real tDCS will be delivered to patients randomized in the intervention group ($n = 29$) using the Starstim8 device (Neuroelectronics, Barcelona, Spain). The Starstim8 will deliver a constant direct current to the motor cortex of the ipsilesional hemisphere using a 4x1 HD-tDCS montage [8, 9, 13, 55]. The active anode electrode will be located on the scalp of the ipsilesional motor cortex (C3 or C4 of the 10–20 system) surrounded by four return electrodes (cathode) located at ~ 4 cm from the anode electrode (Fig. 4). The five HD-tDCS electrodes

(NgPiStim, AgCl, 3.14 cm²) will be held in place on the scalp using a neoprene cap and each electrode will be filled with electrolyte gel (Signagel, Parker Laboratories, New-Jersey, USA). Patients will receive anodal HD-tDCS (2 mA) during the first 20 min of the VRT session. Current will ramp up from 0 to 2 mA for 30 s, remain constant for 20 min, and ramp-down to 0 for 30 s.

Patients randomized in the placebo group ($n = 29$) will wear the same equipment during the VRT session and will receive active sham HD-tDCS where the current will ramp up from 0 to 2 mA during the first 30 s, remain constant at 2 mA for 30 s, then ramp-down to 0 during the next 30 s, and remain at 0 for the next 20 min [9,



Fig. 4 Anodal HD-tDCS applied to the ipsilesional primary motor cortex during an ARMEO virtual reality therapy session using the right upper limb. The patient is setup on the ARMEO exoskeleton equipped with the HD-tDCS cap comprising a Starstim NIC-power box delivering the current on the back and 5 electrodes located on the left primary motor cortex in a 4x1 HD-tDCS montage with anode on the C3 location

13]. This kind of active sham procedure provides the same feelings on the scalp as the real HD-tDCS session [8, 9, 55], which has been shown to be an optimal method for blinding of the stimulation [28, 56].

Before and after each 30-min VRT session (real or sham), subjects will be asked a few questions relating to the sensations on the scalp, which will be part of the pain and fatigue assessments (see “Secondary outcome measures” section). More specifically, patients will be asked if they feel any headache, stinging, itch, burn, and pain sensation on the scalp region where the HD-tDCS electrodes were located [8, 9].

Blinding of group and stimulation protocols

The randomization administrator of the project will designate 8 stimulation protocols in the NIC2 computer software controlling the Starstim8 device (4 active and 4 sham) and give them a blinded code (A to H). Only the blinded code of the program will be given to the therapist in charge of the rehabilitation to be launched for a specific patient. The Starstim8 device will be set in double-blind mode using the NIC2 software, so that the protocol panel does not show the type of stimulation (active or sham). This way, neither the patient, therapist, investigator, nor outcomes assessor will know which protocol is delivered (quadruple blind study). In order to assess blinding, patients will be asked at the end of the 3 weeks of rehabilitation if they think they were in the real or sham stimulation group. If needed (e.g., severe adverse events), blinding could be unblinded if the patient or the medical staff send a request to the Innovation and Research Department (see “Data management” section for more details).

Description of testing visits and outcome measures

Table 2 presents the timing of the testing visits and outcome assessment measures. The baseline assessment (pre-test) visit (V1) will take place on the first day of the 3-week in-patient hospital rehabilitation stay. A specialist trained therapist will run the clinical assessments (WMFT, FM-UE, Box and Block Test (BBT), Bell’s test, MMSE, Barthel Index (BI); more details in the “Clinical data and outcome measures” section). Patients UL kinematics and motor cortical region activation will then be evaluated by one of the investigators on three functional motor tasks: a seated reaching task (Proximal Arm Non-Use, PANU), a circular steering task, and the Ladybug game of the Armeo VRT platform used for rehabilitation. The next day (day 2), patients will start the standard in-patient stroke rehabilitation program that will last for 13 complete days (excluding weekends) over 3 weeks.

The post-test visit (V2) will take place the last day of the 3 weeks (day 19); the post-test will be identical to the pre-test. The 3-month visit (V3) will take place 3 months after the end of the rehabilitation program (day 19) for a retention test and will be identical to the pre-(V1) and post- (V2) tests.

Patients will be given actimetry bracelets to be worn on each UL to measure UL activity for 7 days before V1, for 7 days after V2, and for 7 days after V3.

Clinical data and outcome measures

Clinical data

Clinical data will be collected by the medical doctor during the routine clinical visit, including date of birth, age, sex, hand laterality before and after the stroke, date of the stroke, delay from the stroke to the inclusion, and characteristic of the brain lesion (type and location).

Table 2 Study testing visits (V1-3) and outcome assessments

Outcome measures	Inclusion visit	Pre-test (V1)	Post-test (V2)	Retention test (V3, 3 months after V2)
Mini Mental State Examination	X			
Boston diagnostic aphasia examination	X			
Bell’s test	X			
Wolf Motor Function Test		X	X	X
Fugl-Meyer Upper Extremity		X	X	X
Box and Block Test		X	X	X
Barthel Index		X	X	X
Actimetry		X	X	X
Proximal Arm Non-Use (PANU) ^a		X	X	X
Reaching task (Kinematics and EEG/fNIRS)		X	X	X
Circular steering task (Kinematics and EEG/fNIRS)		X	X	X
Lady bug test (Kinematics and EEG/fNIRS)		X	X	X

^aProximal Arm Non-Use will be assessed during the reaching task
EEG Electroencephalography, fNIRS Functional near-infrared spectroscopy

Treatment, medication, and health events will also be reported. The source documents are the original data, sheets, and files, from which the data concerning the research are copied in the electronic case report form (eCRF) by the clinical investigation centre (CIC).

Primary outcome measure

Wolf Motor Function Test (WMFT) The Wolf Motor Function Test (WMFT [74]) quantifies the motor ability of the UL through 15 timed and function based tasks (i.e., holding a pen, collect paper clips, prehension test) and 2 strength based tasks (arm lifting and hand grip). The speed at which functional tasks can be completed is measured by performance time and the movement quality when completing the tasks is measured by functional ability. The maximum time allowed to complete an item is 120 s. For functional ability scoring, a 6-point ordinal scale is used where 0 corresponds to “does not attempt with the involved arm” and 5 corresponds to “arm does participate/movement appears to be normal”. The WMFT thus gives four scores: (1) a sum of the function score reflecting the movement quality (0–75), (2) a median time score measuring the movement speed (0–120 s), and (3) arm lifting strength (Kg) and (4) hand grip strength (Kg). For our primary outcome analysis, the mean WMFT time and functional ability change scores between the two groups need to be 1.5–2 s for the timed score and 0.2–0.4 points for the functional ability score to be regarded as a clinically important difference [47].

Secondary outcome measures

Fugl-Meyer Upper Extremity test (FM-UE) The motor deficit of the UL will be assessed using the FM-UE [27]. The FM-UE score allows to differentiate proximal UL movements (shoulder, elbow, and forearm; score 44) and distal UL movements (wrist and hand; score 24) totalling 66 points. The results of the scoring system of the FM-UE enable the classification of the patient as having mild ($\geq 40/66$), moderate (between 21/66 and 39/66) or severe ($\leq 20/66$) UL impairment. The FM-UE has excellent reliability, validity, and sensitivity to change and it is regarded as the gold standard to assess UL impairment [30]. The estimated clinically important difference of the FM-UE scores ranges from 4.25 to 7.25 points [57].

Box and Block Test (BBT) The global hand grasping capacity will be assessed using the BBT [52]. The BBT requires the patient to move as many 2.5 cm³ cubes in 60 s (with only one cube been displaced at the time) from a box compartment to another separated by a 15.2-cm-tall partition using the paretic hand and then with the non-paretic hand. Only one trial is given. The

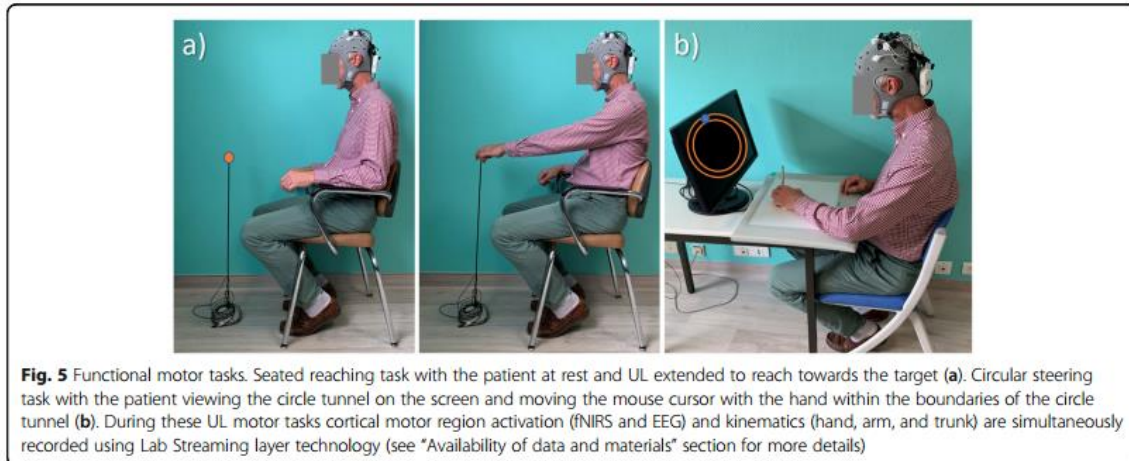
patient score is equal to the number of these cubes transported in 60 s. For healthy subjects, the score at the BBT is between 75 and 80 cubes displaced in a minute. For our population, the smallest real difference before and after intervention is of five or six cubes [14].

Barthel Index (BI) The activities of daily living will be assessed with the Barthel Index (BI [51]). BI assesses the patient’s level of independence to perform ten basic life activities: eating, bathing, personal care, ability to dress themselves, motility, urinary regularity, bathroom use, chair-bed transfer and inversely, mobility, and climbing stairs. The score generated varies from zero (totally dependent) to a maximum score of 100 (totally independent).

Actimetry assessment of paretic UL use in ADL The actual use of the paretic UL in ADL in their own house environment will be assessed continuously over a 7-day period (prior to V1; after V2; after V3) with two wrist worn actimetry bracelets (AX3, Newcastle Helix, UK) on the paretic and non-paretic UL [3]. The two actimetry bracelets record 3D acceleration (± 8 G, 50 Hz) to get objective measures of the actual functional use of the paretic UL in the activities of daily living. The different measures will be the UseRatio (functional use ratio between the two UL), the Use (number of functional movements by the paretic UL), the intensity of paretic UL movements, and the actimetry profile of the different activities using the paretic UL [3, 44, 46, 58].

Proximal Arm Non-Use (PANU) score The non-use of the paretic UL will be quantitatively assessed by the Proximal Arm Non-Use (PANU) score (0–100% [4, 5]) during a seated arm reaching task using kinematic measurements (see “Functional motor tasks” section for details). The PANU score quantifies the shoulder-elbow joint non-use that a patient can voluntarily cancel [5] and has good reliability and repeatability [4]. The PANU score of 6.5% is the limit beyond which we can consider the patient having proximal arm non-use [5].

In the seated arm reaching task (see Fig. 5a), patients will be comfortably seated on a chair with armrests. A target is located in front of them (centred in relation to the body) at a distance such that the base of the metacarpal of the index finger touches the target when the elbow is extended, the shoulder at $\sim 30^\circ$ of flexion and the back resting on the chair. Patients will have to reach the target in two conditions: (i) spontaneous condition, where patients are free to use trunk flexion compensation as they spontaneously do, and (ii) maximal condition, where patients limit trunk movements with the help of a light tactile feedback from the therapist to minimize trunk movements. A practice trial will be done



to familiarize the patients on the timing of reaching (~ 5 reaches/20 s based on pilot testing) by following a recorded voice of investigator to start and return phase of the reaching movement. After a 2-min rest period, the patients will be required to repeat the reaching movements first with the paretic UL then with the non-paretic UL over 3 trials (20 s with 20 s rest between trials). The spontaneous condition will be undertaken first followed by the maximal condition. Kinect V2 (Microsoft, USA) and LSL-Kinect software (see “Availability of data and materials” for details) will be used to stream and analyse the UL kinematics to calculate PANU score and other kinematic variables according to the methods outlined in our previous work [4].

Other/exploratory outcome measures

Functional motor tasks The experimental setup for the Seated Reaching and Circular Steering tasks will allow synchronous measurements of motor cortical region activation (functional near infrared spectroscopy-fNIRS and electroencephalography-EEG) and UL kinematics using lab streaming layers (LSL, <https://github.com/labstreaminglayer/App-LabRecorder>).

In the circular steering task (see Fig. 5b), a computerized version of a circular steering task (LSL-Mouse; see “Availability of data and materials” for details) based on the speed–accuracy trade-off [8] will be used to determine performance improvements of the paretic UL. Patients will be comfortably seated in front of a table with a graphical tablet (A3 size, Wacom, Kazo, Japan) and stylus moulded onto a mouse pad for ease of hand placement for stroke patients. A 24-in. display screen placed behind the tablet will show the circular tunnel and a cursor matching the location of the stylus on the tablet. The patient’s hand will be placed at a location of the

tablet corresponding to the top of the circle tunnel allowing comfortable elbow extension without trunk flexion from the chair. The instruction to the patient will be to move the cursor within the circular tunnel for 20 s, as fast as possible and some errors hitting the tunnel walls are allowed. Biasing speed over accuracy of movements is emphasized in the circular steering task to allow maximum potential of patients to gain benefit from anodal tDCS of the ipsilesional motor cortex [8, 31]. A practice trial will be provided to the patient where they will be able to see their errors online and movement path such that the investigator will inform the patient to speed up the movement if errors are less than 15% (based on pilot testing). After a 2-min rest period, the circular steering task will be repeated over 3 trials (20-s task interspaced by 20-s rest) first with the paretic UL followed by the non-paretic UL.

In the index of performance (IP), speed and accuracy will be calculated as in our previous work [8]. Additionally, trunk displacements will be recorded using the LSL-Kinect and trunk compensation will be determined.

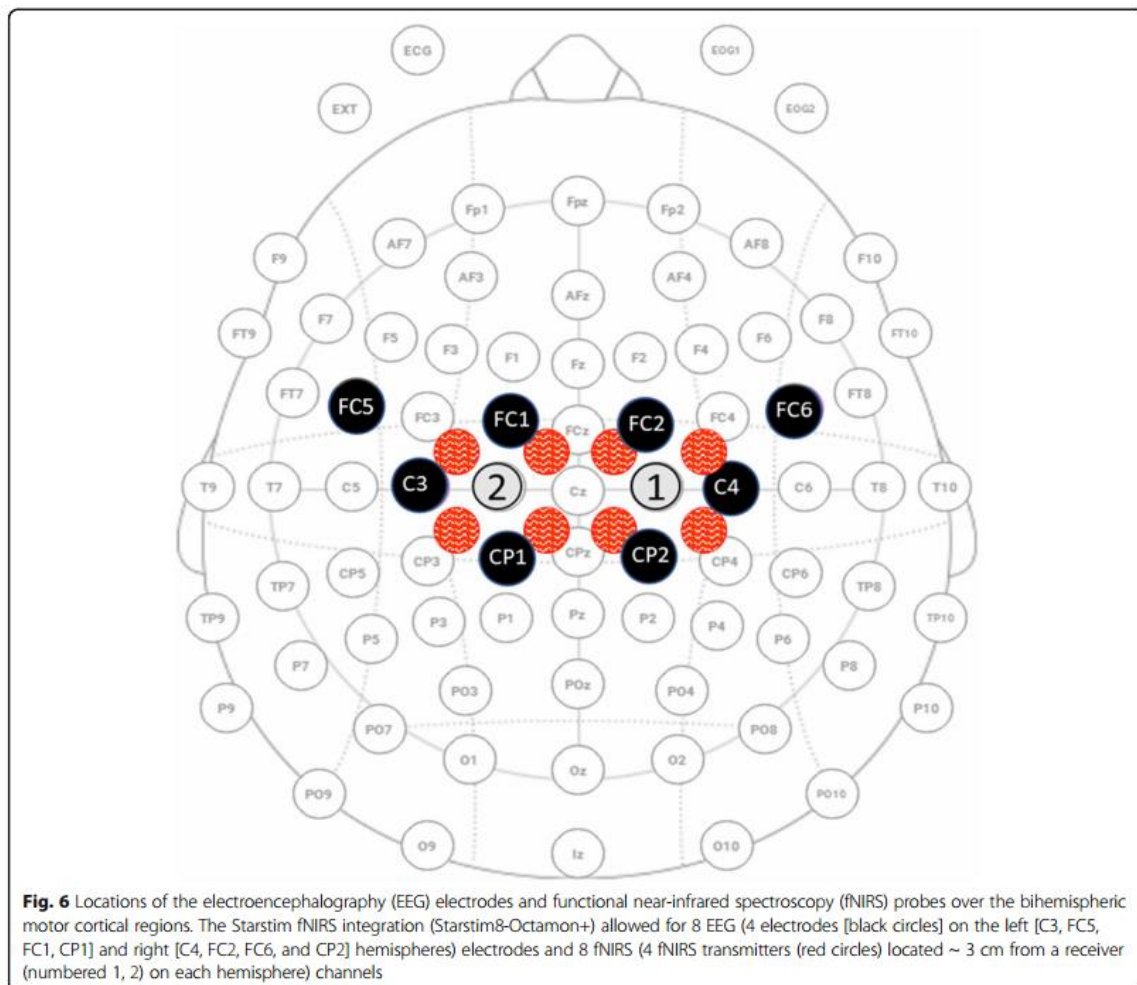
In the Armeo Ladybug game (see Fig. 4), the Ladybug game on the Armeo exoskeleton will allow changes UL movement performance and motor cortical region activation to be determined from a task that will be used during the 3-week combined VRT and anodal HD-tDCS program. The ladybug task will require the patient to “catch” a series of 48 Ladybugs appearing one after the other at different positions on the display screen in less than 3 min. The UL kinematics will be recorded by the Armeo software, which will be analysed to determine the variability trajectory of the end effector to reach the target. Performance metric of the speed and smoothness of UL movements will be based on our previous work [64].

Motor Cortical region activation (fNIRS/EEG) Ipsilesional and contralesional motor cortical region activation will be measured during the 3 functional motor tasks (Seated reaching task, Circular steering task, and Armeo ladybug game) using a Starstim fNIRS integration (Starstim8, Neuroelectronics, Barcelona, Spain; Octamon+, Artinis Medical Systems, the Netherlands) that allows combined EEG and fNIRS measurements with the same neoprene cap used for the HD-tDCS setup. The 8 EEG electrodes and 8 fNIRS channels will be configured above the left and right motor cortical region (around C3 and C4 electrode locations, respectively on a 10–20 system; see Fig. 6).

EEG measures functional brain activity by detecting the variations of electrical fields created by neuronal activation, while fNIRS allows indirect measurement of neuronal activity by monitoring local changes in the oxygenated (O₂Hb) and deoxygenated (HHb) haemoglobin

concentrations in the cerebral microcirculation based on neurovascular coupling mechanism [2, 59]. These two imaging methods have previously been independently used to evaluate changes in motor cortical region activation during functional movements following stroke rehabilitation programs [7, 18], and fNIRS has already been tested and validated during various UL tasks by our team (reaching task in [6]; force task in [18] and in [20]).

In fNIRS analysis, changes in the average, peak, and area under the curve values of the concentration of O₂Hb and HHb in the ipsilesional and contralesional motor cortical region will be determined during the 3 functional UL movement tasks. In addition, a laterality index (LI) will be calculated for each task and trial [20] to determine whether sensorimotor cortex activation, based on O₂Hb concentration, during the task is mainly contralesional or ipsilesional. The LI will be calculated



from the ratio of ipsilesional and contralesional O₂Hb concentration, which varies between - 1 (purely contralesional activation) and + 1 (purely ipsilesional activation [18]).

In EEG analysis, changes in sensorimotor cortex neural oscillations will be measured by the magnitude and ratio of alpha- and beta-frequency power in both ipsilesional and contralesional motor cortical regional at rest and during the 3 functional UL movement tasks. The event-related desynchronization (ERD) of the alpha-motor mu rhythm (8–12 Hz) and of the low beta rhythm (12–20 Hz) will be calculated at the start of each trial. These specific band frequencies are well known to be involved during UL movement for healthy subjects but also for stroke patients [7].

Pain and fatigue of the paretic upper limb Before and after each VRT session, pain and fatigue of the paretic UL during movement will be collected using a visual analogue scale (VAS). The VAS consists of a straight line measuring 10 cm, with 0 cm corresponding to the absence of pain/fatigue and 10 cm corresponding to maximum pain/fatigue.

Perceived exertion Perceived difficulty will be evaluated after each VRT session using the Borg scale of perceived exertion [12]. The Borg scale extends from 6 “no feeling of exertion,” to “very, very hard,” which rates a 20.

Data management and monitoring

During the trial, the sponsor of the project, Montpellier University Hospital (contact: Director of Innovation and Research Department) will be responsible of monitoring the study.

Collecting and data management

The participant will only be identified by a unique identification number, the first letter of the name, the first letter of the first name, his gender, and the year of birth. An identification list of subjects will be kept in the investigator’s file. The investigator will ensure that the anonymity of each person participating in the study is guaranteed. Information will be collected for each participant in a standardized observation booklet filled out by the investigator or the co-investigator.

The source documents are the original documents, data, and files, from which the data concerning the research participants are entered in the electronic case report form (eCRF) by dedicated employees at Montpellier University Hospital. The investigator undertakes to authorize direct access to the source data of the study during control, audit, or inspection visits. Data from the actimetry, from the Armeo and from the functional motor tasks (kinematics, performance, EEG/fNIRS) will

be extracted from the local password-protected computers and stored on the EuroMov centre private server that can be accessed only by the registered investigators (KB, CM, DM, MM, SP, PJ, GD) with reinforced authentication during the duration of the project. All data will be checked monthly by the PI to ensure that all protocols and ethical guidelines for data collection and analysis are followed.

Study data are entered through the e-CRF developed using ENNOV CLINICAL software, which allows real-time data quality control. In order to meet regulatory requirements, this software complies with the recommendations concerning computerized systems for the management of clinical trials and electronic signature and standards. Connection is made by a unique password and identifier specific to each user, which will only give him access to his patients’ data. An audit function is integrated into the software, allowing traceability of the data collected as well as the modifications made. The encrypted data will then be transmitted to the department responsible for data management via a secure internet connection. The eCRF must consist of all the information required by the protocol.

The individual data necessary for the analysis of the study will be:

- Entered into e-CRFs as they are obtained, whether they are clinical or para-clinical data
- Anonymized by the investigator (the participant will be identified only by a unique identification number, the first letter of the name, the first letter of the first name, and the year of birth; an identification list of subjects will be kept in the investigator’s file)
- Authenticated by an electronic signature of the investigator
- All entered; therefore, the missing data must be justified

First, the data entered in the e-CRF is checked and validated by the Clinical Research Associate (CRA) from the source documents. Secondly, the data manager performs additional computerized consistency tests based on the presence of non-standard, missing, aberrant, or inconsistent data and which are performed regularly during patient recruitment and follow-up. All consistency tests are defined in advance in specifications proposed by the data manager and validated by the investigator, the statistician, and the CRA. Each inconsistency identified on the eCRF (“Queries”) is the subject of a request for correction or justification from the investigator (response to “Queries”). The latter undertakes to make himself available to the members of the research team and to provide them with all the additional information required to resolve these errors. This

information is reported in the study database. Once the study is complete, namely the data required for the protocol and any additional data entered (self-questionnaires), the data monitored and validated, the study database is frozen.

The maintenance of the database is the responsibility of the Clinical and Epidemiology Research Unit of the Innovation and Research Department of the study sponsor. The data is kept in an ASCII type format.

The data encoding is integrated into eCRFs. The computer files and the follow-up of any modification are saved and made available by the Innovation and Research Department of Montpellier University Hospital. The database freezing is carried out according to the Innovation and Research Department procedures. The freeze is documented by a database freeze certificate. It takes place once all the data is verified and the corrections requested from the investigators are obtained.

The closure of the trial including the closure of the centres will be carried out in accordance with Good Clinical Practice and International Conference on Harmonization. The medical, administrative, and observation records (all study-related documents) will be kept for the duration of the study, then archived in locked filing cabinets at the PRM department of Montpellier University Hospital, for a minimum period of 15 years after the end of the project.

Monitoring and quality control

The project will be monitored by the CRA. Appropriate monitoring will be implemented based on a risk grid related to the project. In accordance with this grid, the CRA will carry out regular follow-ups of the project's investigation centres (establishment visit, follow-up according to the rhythm of inclusions and a closing visit). All checks will be the subject of a monitoring report by written report (traceability of visits). The investigators agreed to comply with the requirements of the sponsor and the competent authority with regard to an audit or inspection of the research. The audit might be applied to all stages of research, from the development of the protocol to the publication of results and the classification of data used or produced in the context of the research.

Adverse events management

Any adverse events (i.e., muscle or joint pain, syncope, falls and injuries) or serious adverse events (SAEs, i.e., any incident requiring hospitalization) during the HD-tDCS/VRT sessions or testing protocol will be reported to an investigator by filling out the Incident Report Form (IRF). All adverse events will be also recorded, treated, and evaluated upon signing of the consent and until the end of the patient's participation in the study

and/or the end of the collection of adverse events. The Innovation and Research Department will (1) assess the causal link between the serious adverse event and the research; (2) assess whether the adverse reaction is expected or unexpected, using the reference document, the protocol in force for this study; and (3) declare all serious and unexpected adverse reactions within the regulatory deadlines to the competent Health Authorities and the Ethics Committees concerned and informs the investigators at intervals appropriate to the research. Given the type of research (interventional research involving category 2 humans), no annual safety report is planned for this study and given the low risks added by the study, an independent oversight committee will not be established for this study.

Statistical analysis

Sample size

Allman et al. [1] reported that compared to sham, real anodal tDCS (1 mA, conventional montage, ipsilesional motor cortex) combined with 9 days of UL rehabilitation in chronic stroke patients had a moderate effect size $d = 0.4$ on the WMFT at 3 months after the intervention. In the meta-analysis of Chhatbar et al. [16], UL motor recovery (FM-UE) in a chronic stroke population was superior in the group receiving a real tDCS (in comparison to sham) with higher current density and smaller electrode size (large effect size $g = 1.23$). Because we will use anodal HD-tDCS with a higher current density (2 mA) and longer rehabilitation dose (13 days) in chronic stroke patients, we estimate that our protocol should have an effect size of $d = 0.8$ on the WMFT at 3 months. Using an alpha bilateral risk of 5% and a power of 80%, 26 patients per group are needed for analysis. If we count a loss of 10% of the patients, we will have to recruit 58 patients ($n = 29$ per group).

Statistical method

Statistical analysis will be performed using the latest version of the free R software. A p -value of 0.05 will be considered significant for all analyses. All outcome measures will be assessed at V1, V2, and V3. The primary outcome will be the difference between both groups (*intervention, placebo*) at V3 on the WMFT. The secondary outcomes will be the changes between V1 and V2 (learning) and between V2 and V3 (retention) for both groups.

Descriptive analysis

Analysis will be done on the intent-to-treat sample population.

All patients' characteristics at pre-test (V1), post-test (V2), and retention test (V3) will be described according to the randomization group. Qualitative variables will be described using frequency and percentages of each class.

Quantitative variables will be described using median and quartiles.

Primary outcome measure analysis

The aim of the primary outcome analysis will be to compare the functional motor capacity of the UL (WMFT) in the intervention group comparatively to the placebo group at V3. The normality of the data from the WMFT will be analysed by the Shapiro-Wilk test. The variance homogeneity will be assessed using the Bartlett test. If the normality is respected, a parametric Student *t*-test will be performed for mean comparisons. If the distribution of the data is not normal, a non-parametric Wilcoxon signed-rank test will be used.

Secondary outcome measures analysis

The secondary outcome measures (FM-UE, BBT, PANU, BI, and actimetry) will be used to assess the changes in UL impairment, function, non-use, and ADL from V1 at inclusion to V2, and V2 to V3.

Other/exploratory outcome measures analysis

The outcome measures from the 3 functional motor tasks (Seated reaching, circular steering task, Armeo ladybug game) will be used to assess changes in UL performance (e.g., targets reached, IP, speed, accuracy, performance variability) and bihemispheric motor cortical regional activation (e.g., fNIRS-LI and EEG-ERD) from V1 to V2, and V2 to V3. Linear mixed models for the evolution of all these measures will be derived to assess the effect of time (V1, V2, V3) and of group (intervention, placebo). The interaction of group with time will be tested, along with the interaction of group with changes between V1 and V2 and between V2 and V3.

Ethic and reglementary aspect

The research will be conducted in compliance with the French regulations in force, in particular the provisions relating to research involving humans: Law No. 2012-300 of 5 March 2012 relating to research involving humans and its implementing decrees (decree No. 2016-1537 of November 16, 2016, relating to research involving humans, decree No. 2017-884 of May 9, 2017, amending certain regulatory provisions relating to research involving humans), the laws of Bioethics (if applicable), Law No. 78-17 of January 6, 1978, as amended, relating to computing, files and freedoms, the Declaration of Helsinki, and good clinical practices. In the context of this research involving the category 2 human person, the authorization of the competent authority is not required. For information, the sponsor sends the favourable opinion of the CPP and the summary of the protocol to the competent authority.

Prior to carrying out this research involving the human person, the subject's free, informed consent will be obtained after being informed, by the investigator during a consultation and after a sufficient period of reflection. The information intended for trial participants include all the elements defined in Law No. 2012-300 of 5 March 2012 relating to research involving the human person (Jardé Law) and is written in a simple manner, in language understandable by the participant.

The Montpellier University Hospital, sponsor of the study, has taken out a civil liability insurance contract for the entire duration of the study with Newline Syndicate 1218 at Lloyd's guaranteeing its own civil liability as well as that of any party involved in the conduct of the trial, regardless of the nature of the links between the participants and the sponsor.

The data recorded during this research are subject to computer processing under the responsibility of the Montpellier University Hospital, the sponsor, in compliance with the law no. 78-17 of January 6, 1978, as amended relating to the IT, files, and freedoms.

Discussion

The aim of the ReArm project is to evaluate the additional effects on paretic UL function by including anodal HD-tDCS during a 3-week intensive VRT program to supplement conventional therapy in late subacute and chronic stroke patients.

VRT and conventional therapy are equally effective in improving paretic UL function in stroke patients [45]; however, VRT is less labour intensive from a physiotherapy and occupational therapy perspective for the same clinical gains. So therapists can focus on other aspects of rehabilitation as such as providing encouragement, directions, and observing the quality of movement. As such, the PRM departments of Montpellier and Nimes University Hospitals have integrated VRT sessions into conventional therapy sessions as a standard in-patient stroke rehabilitation program. Anodal HD-tDCS is a relatively simple and easily applied NIBS technique that has been shown to enhance motor cortical excitability and plasticity. Anodal HD-tDCS is an ideal candidate to help boost re-learning of paretic UL function in chronic stroke patients. Accordingly, combining anodal HD-tDCS with VRT rehabilitation could further improve neuroplastic effects induced by VRT alone and lead to greater and sustainable clinical gains [11].

The quadruple-blind, randomized, sham-controlled, bi-centre, two-arm parallel, interventional design of the ReArm project was implemented to ascertain whether adding anodal HD-tDCS, a more focalized and intensive form of anodal tDCS, during 3 weeks of VRT (13 × 30-min sessions) that complements conventional therapy (39 × 30-min sessions) would lead to greater and

sustained improvements in paretic UL function. We are expecting a significantly improved functional recovery of the paretic UL for the group receiving real anodal HD-tDCS ($n = 29$) compared to the group receiving sham stimulation ($n = 29$). We will evaluate the effects of the ReArm rehabilitation program using various paretic UL assessments of (i) motor function (WMFT, FM-UE), (ii) prehension dexterity (BBT), (iii) non-use (PANU), (iv) everyday life activities (BI), and (v) motor performance (IP, speed, accuracy, compensation, variability). We will also determine pain, fatigue, and perceived exertion after each VRT session as well as neural biomarkers of paretic UL function by assessments of ipsilesional and contralesional motor cortical region plasticity (fNIRS-LI, amplitude, time to peak and EEG-alpha and beta ERD) during functional motor tasks. Although the primary outcome is based on the clinical assessment of the WMFT at 3 months after the intervention, the ReArm project's multiple secondary and exploratory outcome measures allows to probe other aspects of paretic UL recovery that may benefit from the boost to neuroplasticity afforded by anodal HD-tDCS supplemented during the VRT sessions, which include novel assessments of paretic UL non-use (PANU), use-in ADL (actimetry), and performance (speed and accuracy), including a mechanistic understanding of such paretic UL improvements through neuroplasticity changes in ipsilesional motor cortical regional activation monitored using non-invasive and portable neuroimaging technologies (fNIRS and EEG).

With support from our primary and secondary outcome results, the impact of the ReArm project for the public health care system could be a better efficiency of paretic UL rehabilitation for chronic stroke patients at unchanged or lower cost. With combined HD-tDCS and VRT, we expect a better paretic UL recovery without an increased rehabilitation time commitment, without an increased human resource costs (e.g., physiotherapy and occupational therapy time) but with a relatively minor hardware related costs (tDCS device and consumables) costs. Moreover, this innovative treatment with HD-tDCS is adapted to a majority of patients, since tDCS allows to stimulate the patient while receiving rehabilitation treatment. Therefore, tDCS has a promising clinical potential in post-stroke rehabilitation [61, 63]. Thus, improving the efficiency of recovery for a majority of stroke patients may have an impact on patients' health and on public health costs.

The benefit for the patients taking part of this study could be a better efficiency of the rehabilitation without changing the length of the rehabilitation programs. Indeed, the association of the two methods proposed (anodal HD-tDCS and VRT) could allow, for the same dose of rehabilitation, a better and faster recovery of the paretic UL function. Patients could thus enter in the virtual

spiral of "use it and improve it" aided by the rehabilitation efficiency [38]. This could lead the patient to a better independence on daily life activities and to a better life quality.

Dissemination plan

The results derived from the primary and secondary outcome analysis of this project will be reported in peer-reviewed journal articles and presented at leading national and international conferences. Results derived from the other/exploratory outcome analysis of only the baseline (V1) session will be included in the PhD thesis of CM. Results will be communicated to health professionals and participants through meetings and email/letter, respectively.

Abbreviations

ADL: Activities of daily life; BI: Barthel Index; BBT: Box and Block test; EEG: Electroencephalography; FM-UE: Fugl-Meyer Upper Extremity; fNIRS: Functional near-infrared spectroscopy; HD-tDCS: High-definition transcranial direct current stimulation; NIBS: Non-invasive brain stimulation; PANU: Proximal Arm Non-Use; UL: Upper limb; VRT: Virtual reality therapy; WMFT: Wolf Motor Function Test

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s13063-021-05689-5>.

Additional file 1. SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents.

Acknowledgements

The authors acknowledge Claire Chauveton (Direction Recherche et Innovation), Sophie Bentz, Bernard Moreno, Christel Guiraudie (Direction de la Coordination Générale des Soins), Valerie Driss (CIC), and Lucie Gamon (Clinical Research and Epidemiology unit) from Montpellier University Hospital for their contribution on the administrative aspects of the project. The authors acknowledge the medical doctors and therapists from Montpellier and Nîmes University Hospitals for their commitment in the project for recruitment and training of patients, respectively. We would like to thank Gilles Dusfour from the Cartigen platform at Montpellier University Hospital contributing in the development of the analysis pipeline for the actimetry data. We would also like to thank Benoit Prigent from EuroMov at University of Montpellier for contributing in the development of the LSL-Kinect software application.

Trial status

The study officially began on 12th of November 2020 and recruitment is currently in progress and we expect the end of the recruitment in 2023. This protocol is the second version on 12th of November 2020.

Authors' contributions

KB coordinated the project and obtained funding. KB and MM conceived the project and design, wrote the proposal, and led the protocol development; KB and CM drafted the original manuscript; KB, CM, MM, DM, SP, and IL edited and revised the manuscript; KB, MM, DM, IL, CD, JF, and CM participated in the project design and protocol development; MM, DM, GF, PJ, and SiP developed the experimental setup for the integration of the EEG/fNIRS neuroimaging and kinematics using LSL for the functional motor tasks (including creation of LSL-Mouse and LSL-KinectV2 software); DM, MM, GD, BX, SP, MD, and GF developed the data analysis solution. The authors read and approved the final manuscript.

Funding

The ReArm project is funded by the Direction générale de l'offre de soins (DGOS) in the French Ministère des Affaires Sociales et de la Santé (Programme hospitalier de recherche infirmière et paramédicale-PHRIP-2018-0731). CM and GF are supported by PhD scholarships from the Doctoral School of Human Movement Science at the University of Montpellier. The requested budget was calculated according to the design of the study (number of subjects, number of centres and visits planned/patient and number of specific examinations carried out), the applicable regulations and additional and specific examinations planned in the framework of this study. As a reminder, this study is based, in 2 centres, on the inclusion of 58 patients in total. The design, management, analysis, and reporting of the study are entirely independent of the funding received for the ReArm project.

Availability of data and materials

The full unrestricted dataset will be given to the trial statistician of the project (CD) by the principal investigator (KB). Agreements with EuroMov-DHM laboratory will allow full access to SP for the EEG and fNIRS dataset and DM for the kinematics and actimetry dataset. CM and MM will have restricted access to the full dataset. GD, BX, and GF will have restricted access to EEG, fNIRS and kinematics dataset. The final datasets will be available from the corresponding author on reasonable request. The software applications developed for this project and the most recent version of the software are available from the corresponding author's Github repository (LSL-Mouse, <https://github.com/KarimaBak/LSL-Mouse>, and LSL-KinectV2, <https://github.com/KarimaBak/LSL-KinectV2>) and an archived version on the Zenodo repository (LSL-Mouse, DOI <https://doi.org/10.5281/zenodo.4297675>; LSL-KinectV2, DOI <https://doi.org/10.5281/zenodo.4300182>). Other materials used in the project (e.g., consent forms) will be available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The French Research Ethics Committee (Comité de Protection des Personnes- CPP SUD-EST II) approved the study protocol (No. ID-RCB 2019-A00506-51) on September 30, 2019. Should there be any changes to the protocol (i.e., changes to eligibility criteria, outcomes, analyses etc.), an ethics amendment form will be submitted to the Ethics committee for consideration and approval. Before randomization, all participants will be requested to provide written informed consent. This consent will be obtained by an investigator.

Consent for publication

The identifying images or other personal or clinical details of participants that compromise anonymity will not be published. The participants in the images contained in Figs. 2, 3, 4, and 5 have given their informed consent to the publication of these images.

Competing interests

The authors declare that they have no competing interests.

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Received: 9 March 2021 Accepted: 5 October 2021

Published online: 26 October 2021

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6.3. More details about kinematics

6.3.1. Paced-reaching task (in collaboration with K. Bakhti and G. Faity)

The paced-reaching task kinematics analysis was done based on previous work and PhD thesis which validated the kinematics parameters (Bakhti et al., 2017; Faity et al., 2022; K. Bakhti PhD thesis, 2017) and the use of a Kinect[®] v2 (Microsoft, USA; Bakhti et al., 2018). The Kinect provides a marker-less measurement of 3D joint kinematics (X, Y, Z positions of 25 joints on a skeleton) using a combination of 3 sensors (RGB colour camera, depth sensor and infrared sensor) at a sampling rate of 30Hz (Zhang, 2012). The 3D positions were recorded thanks to a home-built software (LSL-Kinect, developed by P. Jean at the EuroMov-DHM laboratory; LSL-KinectV2, <https://github.com/KarimaBak/LSL-KinectV2>). Data processing were performed using SCILAB (V 6.0.2). Kinematics parameters were calculated using the trunk, shoulder, elbow, hand displacement and the movement time. Below is the description of the parameters used in the present thesis.

- **Proximal-arm use (PAU, in %; see figure 14)**

The PAU index corresponds to the percentage of the arm extension used to realize the reaching movement and refers to the contribution of the arm to the hand movement toward the target. It is calculated with the change in distance to the target during the reaching movement, for the trunk and for the hand (Δ_{Trunk} and Δ_{Hand} in Figure 14). PAU calculation is $PAU = \frac{\Delta_{\text{Hand}} - \Delta_{\text{Trunk}}}{\Delta_{\text{Hand}}}$.

- **Proximal-arm non-use (PANU, in %; see figure 14)**

The PANU index corresponds to the difference between spontaneous arm use (i.e., free reaching movement without any constraint) and the maximal arm use (i.e., patients limit trunk movements with the help of a light tactile feedback). It quantifies the shoulder-elbow joint non-use that a person can voluntarily cancel with a score going from 0% to 100% (note that the score of 6.5% is the limit beyond which we can consider the person having proximal arm non-use; Bakhti et al., 2017). This score is calculated using the subtraction of the spontaneous proximal-arm use (sPAU, figure 15) to the maximal proximal-arm use (mPAU, figure 14).

- **Velocity components (mm/s) – mean, peak velocity, number of velocity peak**

Even though the task was paced at a rhythm of a reaching movement every 4 seconds (2 seconds to do the reaching movement), the speed strategy to do the reaching movement could vary among participants and conditions to target and back within the 4 s period allocated per movement. These variables were calculated based on the hand displacements.

- **Trunk compensation parameter: range of trunk anterior flexion and shoulder displacement (°)**

Is calculated as the difference, in degree, between the end and the beginning of the reaching movement. It does represent the use of the trunk (compensation) to realize the reaching movement (i.e., more shoulder displacement is associated to more trunk flexion).

- **Arm use parameter: range of elbow extension and of shoulder adduction (°)**

It is calculated as the difference, in degree, between the end and the beginning of the reaching movement. It does represent the use of arm extension to do the reaching movement.

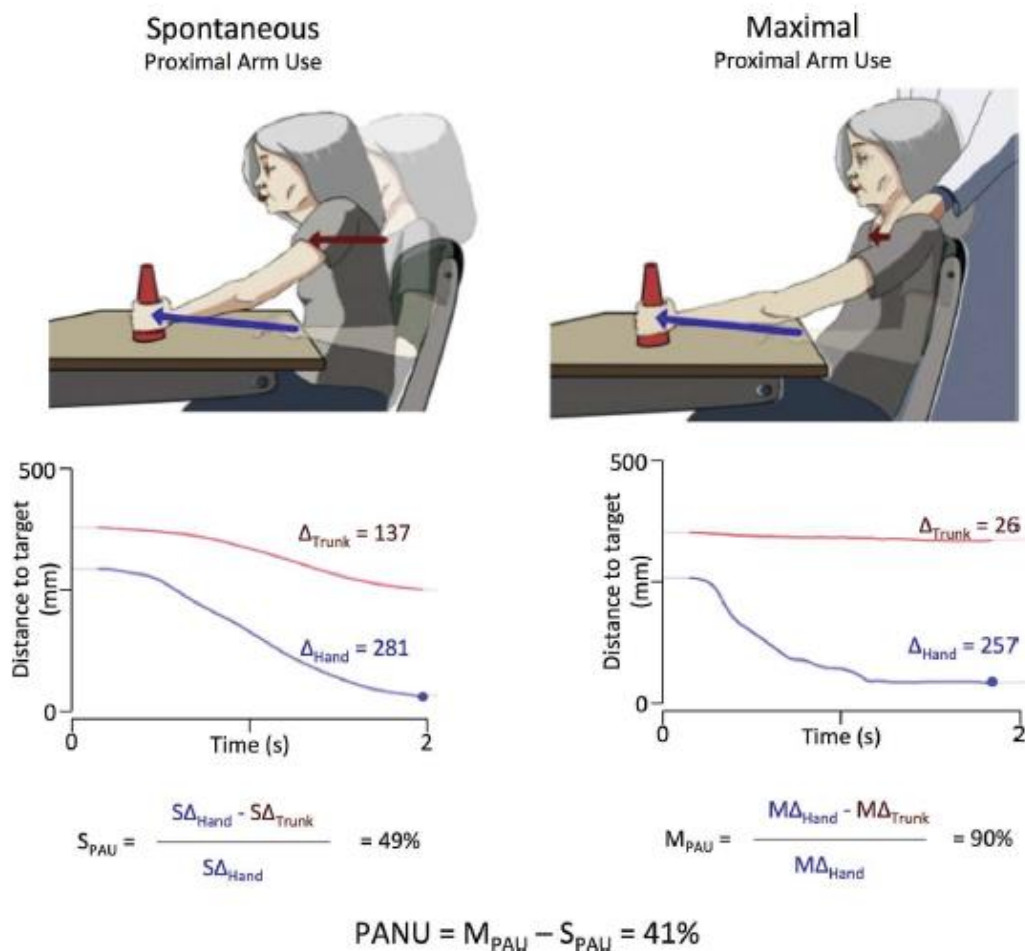


Figure 14 - Proximal-arm non-use evaluation.

This figure presents the setup of the PANU assessment. In this example of a patient using her paretic arm, we can see the use of trunk during the spontaneous reaching that is reduced during the maximal reaching. The graphs below are showing the distance to the target as a function of time. Blue line represents the hand movement and red line represents the trunk movement. Δ_{Trunk} and Δ_{Hand} are the changes in distance to the target during the reaching. Proximal arm-use (PAU) is calculated in spontaneous and maximal condition and PANU score represents the difference between maximal and spontaneous arm-use. *Figure from Bakhti et al. (2017)*

6.3.2. Circular steering task (in collaboration with G. Faity and D. Mottet)

The analysis of the circular steering task was done with SCILAB. The 2D (X, Y) position of the mouse on the pad was extracted thanks to the LSL-Mouse software (developed at the EuroMov-DHM laboratory by D. Mottet, P. Jean, S. Pla, M. Muthalib and K. Bakhti; LSL-Mouse, <https://github.com/KarimaBak/LSL-Mouse>). The recorded variables were the speed (based on the number of laps), the accuracy (based on the bias and the % out of the target) and an index of performance based on a method described below built at the laboratory and described in an internal seminar in May 2020 (G. Faity, D. Mottet). Figure 15 illustrates the parameters used to calculate the performance at this task.

The circular steering task, is, as presented in the methodological paper (Muller et al., 2021), a UL continued visuo-motor task based on Fitts law which is stipulated that the time of movement is linearly increasing with the difficulty index of the task (ID, in bits; Fitts, 1954). In the case of circular movement, the task space could be described in polar coordinates (radius & phase): the task is to “**keep the radius within the tolerance limits while having the highest phase velocity**”. This task relies on the steering law, that is describing the relationship between the time necessary to navigate through a two-dimensional tunnel and the task parameters (Accot & Zhai, 1999). Accot and Zhai (1999) define the task’s ID of a continuous path movement as follow:

$ID = \frac{2\pi R}{W}$, with R as the radius of the circle, $2\pi R$ as the perimeter of the circle, and W as the width of the band, all in length unit

As the deviation from the path is a random process, Crossman (1956) proposed an adjustment of width, taking account the effective situation incorporating noise in the width equation (*noise = distance to center (d) – radius (R)*, with noise, d and r in length unit). In practice, the effective width (We) is depending on the bias (i.e., the perception of the task difficulty, in other words, how the participant re-interpret the constraint of the task; (MacKenzie, 1992).

$We = \sqrt{2\pi e} * SD$, with We and SD (the standard deviation of noise), in length unit

$We = bias * W \Leftrightarrow bias = \frac{\sqrt{2\pi e} * SD}{W}$

D. Mottet and G. Faity (EuroMov-DHM laboratory seminar, 2020) proposed a reevaluation of the ID with the bias, taking account the effective difficulty (IDe), meaning, with the difficulty the subject is following (i.e., effective width more or less larger than the width proposed). For this purpose, they also use the effective radius (Re) which represent the average distance between the

centre of the target and the path. They reformulated it in function of the number of laps, as in our task, participants had to draw circles during a fixed time (MT = movement time), thus, more the participant is fast, more n_{laps} is increasing.

$$ID_e = \frac{2\pi R_e * n_{laps}}{W_e} = \frac{2\pi R_e * n_{laps}}{\sqrt{2\pi e} * SD}$$

Knowing the task ID, we can now look at the index of performance (IP) for the task. According to Fitts law, this ID is fluctuating with MT and IP. IP can thus reflect the participant performance for a given difficulty (Fitts, 1954).

$$IP = \frac{ID}{MT} \text{ with IP in bits/s, ID in bits and MT in s}$$

Finally, in our circular steering task, we can resume it with the effective IP (IPE; Faity and Mottet, 2020):

$$IPE = \frac{ID_e}{MT} = \frac{2\pi R * n_{laps}}{\sqrt{2\pi e} * SD * MT} \text{ (With IPE in bits/s, ID}_e \text{ in bits, MT in s, R in length unit, MT in s and SD in}$$

length unit).

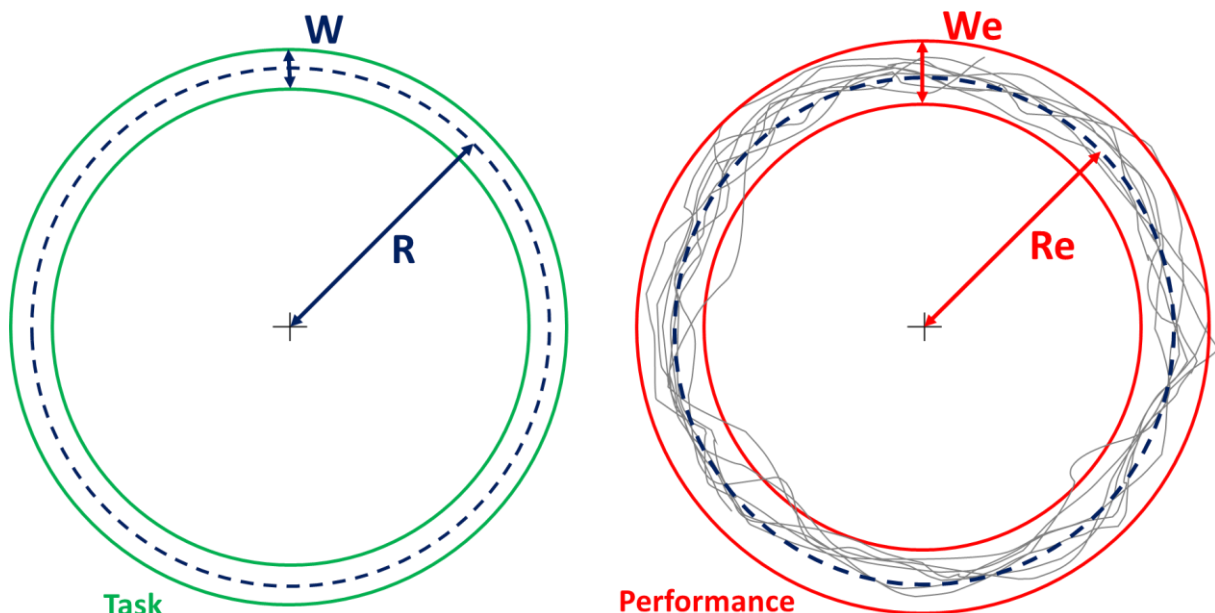


Figure 15 - Circular steering task and parameters to calculate index of effective performance. Representation of the circular task in green (left side) with R the radius of the circular path and W the width of the path. The right panel grey trace is representing the circular path. We is representing the effective width (which you can see is larger than W) and Re is the effective radius. Figure built with G. Faity

6.4. More details about neuroimaging

To synchronize movement and brain activity data, we used a lab-streaming-layer (LSL) application to time-align all the signals recorded (<https://github.com/labstreaminglayer>). Both EEG and fNIRS brain signals recorded were analysed based on the beginning of the task and rest periods as markers. The use of the LSL files (xdf) allows to temporally synchronize these markers in both signals. The Brodmann's areas covered by EEG electrodes and fNIRS probes were extracted via the NFRI function (Lancaster et al., 2000; Singh et al., 2005) using the MNI (Montreal Neurological Institute) coordinates (obtained using a 3D digitizer; Patriot®, Polhemus Inc., USA). The final locations of over the sensorimotor cortices were presented in the first experimental study of this thesis (see table 2 in Muller et al., 2023).

6.4.1. EEG (in collaboration with B. Xu and M. Muthalib)

The EEG used was an 8-channels design sampled at 500 Hz (Starstim 8, Neuroelectronics, Barcelona, Spain). All EEG analyses were performed under MATLAB (version 2021.1) with EEGLAB functions (version 2021.1; <https://eeglab.org/>; Delorme & Makeig, 2004). The previously presented EEG montage (see figure 6 of Muller et al., 2021) included 8 channels, and frequency analysis was completed. We decided to calculate event-related spectrum perturbation (ERSP) to detect, in the Alpha (8–13 Hz) and Beta (14–29 Hz) band, power desynchronization (i.e., power decrease) in motion and synchronization (i.e., power increase) at resting state (see figure 11 in Chapter 3). These two bands are, in the motor cortex, related to state changes from motion to resting state.

The analysis was developed based on another study seeking also to evaluate the EEG power modification in the primary sensorimotor cortex (SM1) during UL tasks (Nakayashiki et al., 2014).

First, data was converted from nanovolts to microvolts, re-referenced with the channel-average method and further down-sampled to 250 Hz. It was then filtered using a band-pass filter between 0.3 and 50 Hz. All signals were manually reviewed, using three visualisations: i) raw signal; ii) re-referenced signal; and iii) filtered signal. Those affected by noisy channels, noisy trials, and trials with abnormal movement were rejected. To obtain event-related shifts in the power spectrum, we used ERSP analysis (Makeig & Inlow, 1993). A time window of 1s (i.e., 250 samples) was chosen to perform the short-term Fourier transform (STFT). It allowed to

obtain the instantaneous power spectrum at every time window (for more details see (Kehtarnavaz, 2008), 7.2. *Short-Time Fourier Transform*). The ERSP in the alpha (8-13 Hz) and beta (14-29 Hz) band were represented as a percentage of the average power changes in these specific time-frequencies relative to a baseline period (i.e., the rest for ERD or the movement for ERS). A baseline correction was applied by subtracting the mean power changes in a 1 s baseline period from each spectral estimation, in order to normalize the ERSP. The relative power change was calculated as follow using the instantaneous power spectrum (P_n ; Nakayashiki et al., 2014):

$$P_{rest} = \frac{1}{|T_{rest}|} \sum_{n \in T_{rest}} P_n,$$

$$P_{task} = \frac{1}{|T_{task}|} \sum_{n \in T_{task}} P_n,$$

ERD calculation

$$RP = \frac{P_{task} - P_{rest}}{P_{rest}} \times 100$$

ERS calculation

$$RP = \frac{P_{rest} - P_{task}}{P_{task}} \times 100$$

P_{rest} and P_{task} are the mean power spectra respectively during rest period (T_{rest}) and task period (T_{task} , see figure 16). Mean ERSPs were calculated and averaged by tasks (reaching and circular steering) and hand conditions (dominant and non-dominant) during rest and movement periods. All pre- and processing steps of EEG treatment are resumed in figure 17.

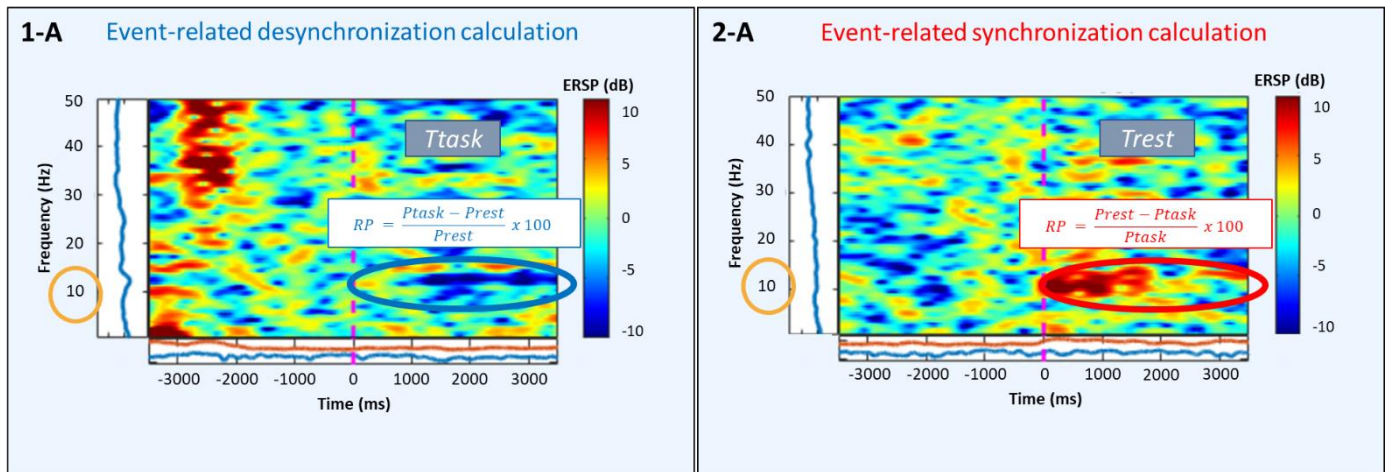


Figure 16 – Event-related desynchronization and synchronization calculation.

On left panel (1-A), you can see how the relative power change (RP) at the beginning of task period (T_{task}) is calculated and the dark blue stains indicates that at this frequency (around 10 Hz) there is a power diminution (i.e., desynchronization). On the right panel (2-A) you can see how RP is calculated at the beginning of rest period (T_{rest}) and the red/orange stains indicates that the power at this frequency (around 10 Hz) is increasing (i.e., synchronization).

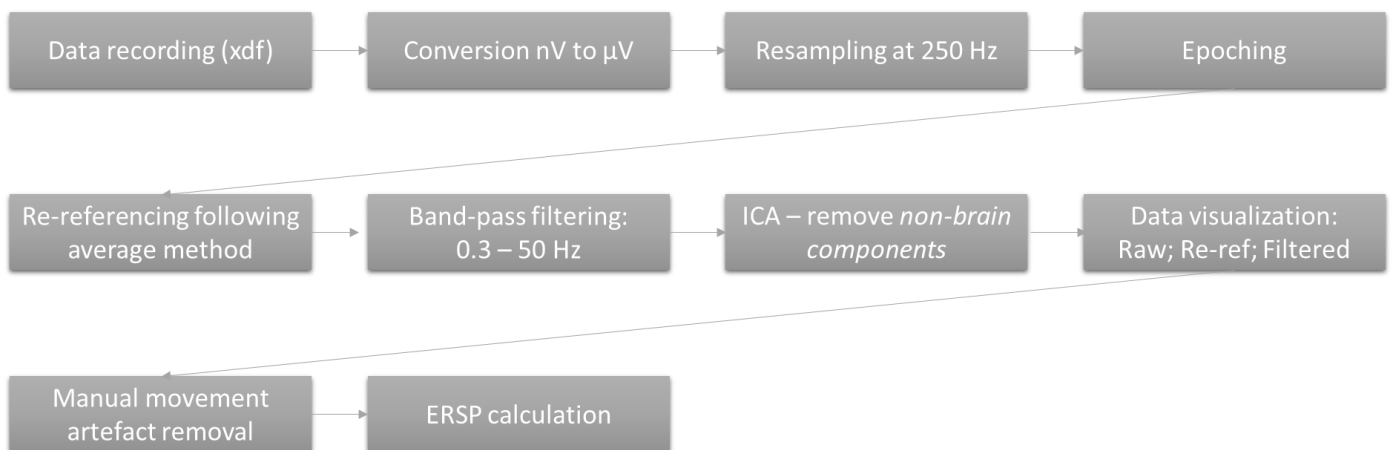


Figure 17 - Summary of EEG pre- and processing steps.

6.4.2. fNIRS (in collaboration with G. Dray, M. Muthalib and S. Perrey)

A continuous-wave fNIRS system using two wavelengths was used for measuring the changes in HbO₂ and HbR overlying the left and right SM1 at a sampling frequency of 10 Hz (Octamon+, Artinis Medical Systems, Netherlands). All fNIRS raw data analysis was undertaken using HOMER toolbox on MATLAB (Homer2 NIRS processing package; Huppert et al., 2009).

Following previously used pipeline (Besson et al., 2019; Delorme et al., 2019), optical density time series were first converted into relative concentrations of ΔHbO_2 and ΔHbR using the modified Beer-Lambert law corrected by a differential pathlength factor depending on the age of the participant (Duncan et al., 1996, function `hmrOD2Conc` of `Homer2`). Data were then band-pass filtered (Low cutoff: 0.08- high cutoff: 0.009Hz; function `hmrBandpassFilt` of `Homer2`) to eliminate physiological confounds such as low-frequency drift, Mayer-wave systemic oscillations, breathing rate and heart rate components (Menant et al., 2020). Onset of each movement was then identified. Motion artifacts were visually checked and removed manually when a sudden change of ΔHbO_2 and ΔHbR traces were observed. The corresponding epoch and/ or optode was then excluded. We did not apply systemic physiology artifact correction for fNIRS signals by means of a short distance channel regression procedure. We adopted in our studies the following approaches when defining the experimental setup to minimize false positives, as our data were not presenting too many artifacts and as it remains a robust way to prevent any inclusion of artifact signal (Muller et al., 2023). Each block of 5 movements was then corrected with a zero-baseline value based of the onset of the first movement. The relative concentration changes of HbO_2 and HbR were computed within the motor task intervals (0-20 s) to reflect the immediate hemodynamic response (Delorme et al., 2019). After having verified the neurovascular coupling occurrence during functional movement (i.e., rapid increase in ΔHbO_2 with a lower-amplitude reduction or flat signals in ΔHbR), the value and latency of the larger variation (peak), the average and the area under the curve values were computed for each block of 20 s, each participant and for each haemoglobin species. In both experimental studies, we found a positive correlation between area under the curve, average and peak of ΔHbO_2 showing that these three variables are giving similar information of signal magnitude in our cases. Moreover, as ΔHbO_2 is most sensitive for motor task-related hemodynamic changes, the relative changes in peak ΔHbO_2 concentration were employed as the main indicator of brain activity; the time to the peak ΔHbO_2 concentration is also presented. Peak and time to peak of ΔHbO_2 are represented in figure 18. These parameters were averaged by tasks (paced reaching; circular steering) and hand condition (dominant; non-dominant). All pre- and processing steps of fNIRS treatment are resumed in figure 19.

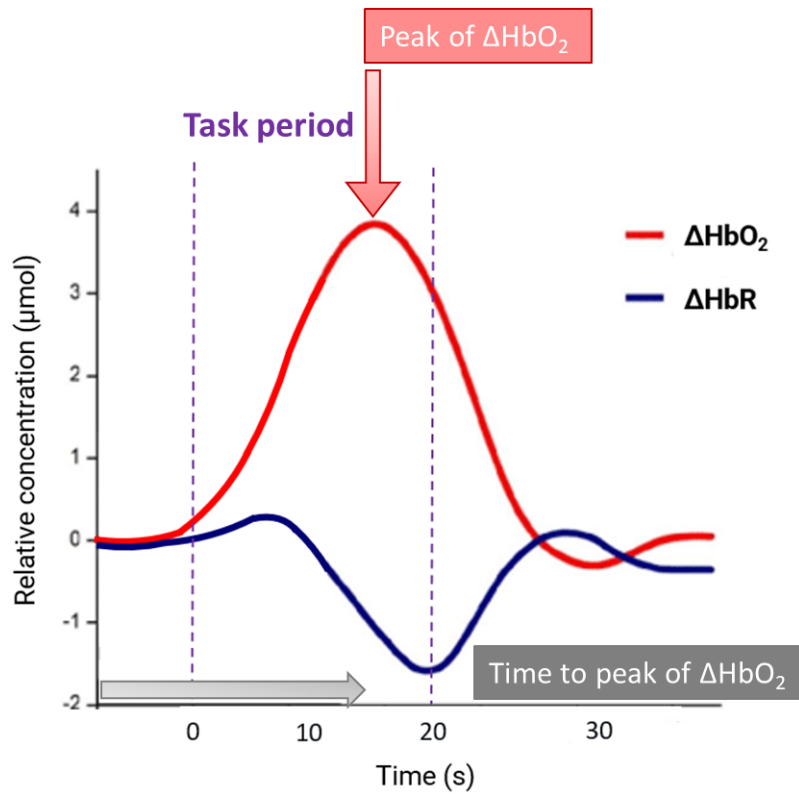


Figure 18 - Representation of ΔHbO_2 peak and time to peak during a hemodynamic response.

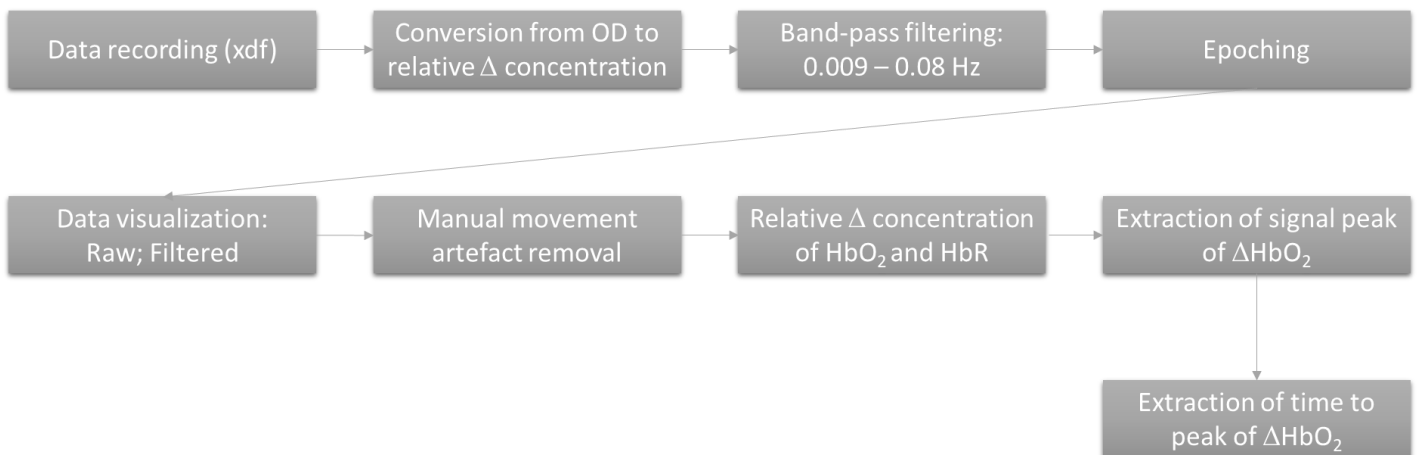


Figure 19 - Summary of the pre- and processing steps of fNIRS treatment.

6.5. Chapter key-points**METHODOLOGY**

- Two functional unilateral tasks involving a complete use of UL joints (i.e., shoulder, elbow, wrist) and able to detect compensatory strategies (i.e., use of trunk flexion).
 - Reaching task – with spontaneous and maximal condition
 - Proximal-arm use and non-use
 - Speed component of movement
 - Circular steering task – with speed-accuracy trade-off
 - Index of effective performance
 - Strategies of movement (i.e., speed, accuracy)
- Two functional neuroimaging methods – easy to combine, to use and providing a good spatio-temporal SM1 view
 - EEG – based on electrical activity
 - 4 channels over each SM1
 - Frequency analysis (ERD, ERS)
 - fNIRS – based on hemodynamic response
 - 4 channels over each SM1
 - Amplitude and time course of ΔHbO_2

NEXT STEP

Application of this methodology to explore the brain and movement modifications with healthy aging and stroke (pathological aging).

Panel 7

Chapter 7: Task-related brain activity and kinematics with healthy aging

7.1. Context and objectives

In the previous chapter, we presented methods to evaluate the task-related brain activity and the movement kinematics. This global methodology was applied in this first experimental chapter to answer to our second objective “the effects of healthy aging on the related brain activity of UL functional tasks”.

In this chapter, we aimed to evaluate the effect of healthy aging on the bilateral sensorimotor (SM1) activation patterns of functional proximal UL movements. In the literature review of this thesis, we presented several models of cognitive aging suggesting compensation and reorganization of the aging brain during the execution of cognitive task but also in few studies, during motor tasks. Nevertheless, there is a clear lack on the literature around the proximal movement, and how its brain-related activity is modified with healthy aging.

For this purpose, we collected the SM1 brain activity during the two previously presented tasks following the methodology depicted in Chapter 6. We included in this first experimental study two groups of healthy people: one young ($n = 21$; mean age = 25.1 ± 4.7 yrs.) and one older ($n = 21$; mean age = 73.1 ± 6.7 yrs.) groups.

This study was published in *Behavioural Brain Research* and the final version of the article is presented in section 7.2. (Muller et al., 2023).

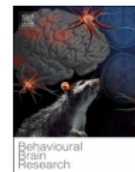
7.2. First experimental study

ARTICLE 2: C.O. Muller, S. Perrey, K. Bakhti, M. Muthalib, G. Dray, B. Xu, D. Mottet, I. Laffont.(2023). **Aging effects on electrical and hemodynamic responses in the sensorimotor network during unilateral proximal upper limb functional tasks.** BEHAVIOURAL BRAIN RESEARCH, 443, 114322. <https://doi.org/10.1016/j.bbr.2023.114322>



Contents lists available at ScienceDirect

Behavioural Brain Research

journal homepage: www.elsevier.com/locate/bbr

Aging effects on electrical and hemodynamic responses in the sensorimotor network during unilateral proximal upper limb functional tasks

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ARTICLE INFO

Keywords:

Motor-control
Neuroplasticity
fNIRS
EEG
Reaching and tracing task
Brain asymmetry

ABSTRACT

Healthy aging leads to poorer performance in upper limb (UL) daily living movements. Understanding the neural correlates linked with UL functional movements may help to better understand how healthy aging affects motor control. Two non-invasive neuroimaging methods allow for monitoring the movement-related brain activity: functional near-infrared spectroscopy (fNIRS) and electroencephalography (EEG), respectively based on the hemodynamic response and electrical activity of brain regions. Coupled, they provide a better spatiotemporal mapping. The aim of this study was to evaluate the effect of healthy aging on the bilateral sensorimotor (SM1) activation patterns of functional proximal UL movements. Twenty-one young and 21 old healthy participants realized two unilateral proximal UL movements during: i) a paced reaching target task and ii) a circular steering task to capture the speed-accuracy trade-off. Combined fNIRS-EEG system was synchronised with movement capture system to record SM1 activation while moving. The circular steering task performance was significantly lower for the older group. The rate of increase in hemodynamic response was longer in the older group with no difference on the amplitude of fNIRS signal for the two tasks. The EEG results showed aging related reduction of the alpha-beta rhythms synchronisation but no desynchronisation modification. In conclusion, this study uncovers the age-related changes in brain electrical and hemodynamic response patterns in the bilateral sensorimotor network during two functional proximal UL movements using two complementary neuroimaging methods. This opens up the possibility to utilise combined fNIRS-EEG for monitoring the movement-related neuroplasticity in clinical practice.

1. Introduction

Decrease in motor performance with aging [1] alters more specifically the daily life tasks involving upper limb (UL) movements (e.g. hand control for reaching tasks; [2]). As the aging population is increasing, understanding the neural correlates linked with UL functional movements may help to better understand how healthy aging affects the level of brain activation and lateralization of the sensorimotor network related to the speed and accuracy of movement [3,4].

In healthy young adults, an asymmetry in SM1 activation patterns have been generally reported for unilateral distal UL movements, where the contralateral hemisphere is more activated than the ipsilateral one [5–7]. This brain asymmetry for UL movement control is understood in

the context of the greater proportion of the corticospinal tract emanating from the contralateral SM1 [8]. Nevertheless, both high handgrip strength, manual dexterity or task complexity can increase substantially the ipsilateral SM1 activation [6,9] and excitability [10], thus reducing the hemispheric asymmetry of the brain.

In healthy people, age-related physiological changes alter the neural circuitry at the structural level, especially in the SM1 [11], the cortico-striatal and the cortico-cerebellar networks [12], and at the functional level with regard to neuronal plasticity [13]. Several models have emerged in the literature to explain these modified brain reorganisation patterns regularly observed in healthy aging during both cognitive tasks and cognitive-locomotor dual tasks. Two major models (compensation-related utilization of neural circuits hypothesis

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<https://doi.org/10.1016/j.bbr.2023.114322>

Received 10 October 2022; Received in revised form 4 January 2023; Accepted 29 January 2023

Available online 31 January 2023

0166-4328/© 2023 Published by Elsevier B.V.

-CRUNCH, [14]; and hemispheric asymmetry reduction in older adults -HAROLD, [15]) suggest in elderly additional neural resources to compensate when facing elevated task requirements due to reduced neural efficiency, and a higher recruitment in the opposite (ipsilateral) hemisphere for the same task, respectively. Hence, a more bilateral brain activation would occur. More recently, brain reorganisation was revealed with hyperactivation of the task-specific motor networks during distal hand-movements in elderly compared to young to maintain the grip performance [4]. In addition, producing unilateral fine hand motor tasks, such as finger tapping tasks, recruits more bi-hemispheric areas for older adults with a greater activation of SM1 [16–18]. With aging, functional movements involving proximal UL joints (shoulder, elbow) are more affected and could present modification in the speed and accuracy components of the movement [2]. Nevertheless, there is no information about the effects of healthy aging on changes in brain activation patterns of the sensorimotor network during unilateral multi-joint proximal UL movement tasks seen in daily life.

In order to evaluate sensorimotor network activation during functional proximal UL movements in real-world settings, two non-invasive neuroimaging methods can be used. First, functional near infrared spectroscopy (fNIRS) relying on the concentration changes in oxygenated (HbO₂) and deoxygenated (HbR) haemoglobin at the cortical regions of interest, has been used to measure sensorimotor network activation during distal UL movements in healthy young adults [6, 19–21] and in older healthy adults [22,23]. A limited number of studies have investigated proximal UL movements, such as reaching movements. Although in healthy adults it has been shown by using fNIRS that the contralateral brain was mainly activated [20], a more bilateral activation pattern is observed in proximal compared to distal UL movements [24]. Secondly, electroencephalography (EEG) measures functional brain activity directly by detecting the variations of electrical currents at the scalp from local electric fields produced by neuronal activity [25]. Event-related power changes in the neural oscillatory activities contained in EEG signals have been used to decode the movement [26]. These power modifications are contained within specific frequency bands of the SM1 (alpha-mu – 8–13 Hz and beta – 14–29 Hz). These oscillations over the SM1 are characterized by a power decrease during movement execution (event-related desynchronization, ERD) while the resting period is characterized by a power increase (event-related synchronization, ERS), which respectively indicate the level of excitation and inhibition in the sensorimotor network [27]. Some studies have shown a bilateral alpha-mu and beta ERD during unilateral hand movements in young and older populations [26–28]. However, a limited number of EEG studies have investigated age related differences during UL movements and found controverted results for ERD [28,29] and for ERS [30,31].

Both fNIRS and EEG methods provide independent non-invasive and portable recordings of brain activation related to movement without any strong movement constraint [32]. Combining the two neuroimaging systems together on a single headset could provide better spatio-temporal information of the brain activation patterns of SM1 over the two hemispheres [21,33], with high temporal resolution of the neuronal and hemodynamic components [34]. The proposed fNIRS-EEG association could highlight the inter-hemispheric reorganisation of both SM1s and the evolution of event-related brain oscillations with aging during miscellaneous unilateral proximal UL movements.

Therefore, the main objective of the present study was to evaluate the effects of physiological aging on the electrical (EEG) and hemodynamic (fNIRS) responses over bilateral SM1 regions during unilateral proximal UL movements. More specifically, we aimed to unveil hemispheric differences in the level of brain hemodynamic and electrical oscillation patterns in young and older adults during unilateral multi-joint UL movements, one with no constraints on performance (paced reaching task) and one that has speed-accuracy constraints (circular steering task). We hypothesised that with aging, the bi-hemispheric electrical and hemodynamic responses during the two proximal UL

movement tasks will be greater. As a secondary objective we wanted to explore aging effects on the brain pattern related to the motor performance in the circular steering task. We expected a lower neural efficiency in the older group due to a greater bilateral brain activation pattern for maintaining reduced motor performance.

2. Material and methods

2.1. Participants

A total of 42 right-handed healthy adults were recruited and assigned to a young or older group of 21 participants (see Table 1). Participants were recruited through students mailing lists for the young group and via local associations for the older one. To be included, participants had to be aged either between 18 and 40 years old (Young group), either between 60 and 90 years old (Old group) and to be right-handed assessed by the Edinburgh Handedness Inventory [35]. Exclusion criteria were the existence of neurological (including a history of traumatic brain injury) or motor disorders at the level of the upper limb (history of tendinous disease, arthritis, surgery). All participants gave informed written consent before participating to the study. In accordance to the Declaration of Helsinki, the study was approved by the local Ethics Committee (EuroMov IRB, permit number 1912B).

2.2. Experimental design

All participants came to the laboratory for a single 1 h session. The experiment took place in a quiet isolated room. The participants were equipped with the fNIRS-EEG neuroimaging systems and then had to perform two functional UL tasks while seated, a paced reaching arm task and a circular steering task. The setup allowed for combined and synchronous recordings of UL kinematics and brain activity (fNIRS and EEG) using lab streaming layer (LSL, <https://github.com/labstreaminglayer/App-LabRecorder>; see *Functional motor tasks* section).

2.3. Functional motor tasks

More details about the methodology of the functional motor tasks are presented in a recent methodological paper (see figure 5 in [36]). The description of the two UL motor tasks in sitting position are as follows:

2.3.1. Paced reaching task

Participants were seated on a chair with armrests and had to reach a target (a ball) in front of them, at 80 cm of height and at a distance allowing a complete extension of the right arm. A Kinect sensor (V2, Microsoft, United-States) was placed in front of them at 1.70 m height and at 1.60 m from the target. Five free movements per block of 20 s were paced by the voice (“go”; “stop”). After one block of practice with each hand, they had to perform the paced reaching task for 3 blocks with their non-dominant hand and then for 3 blocks with their dominant hand. Each block was interspaced by ~20 s of rest. Then, participants performed the same task for 3 blocks with each hand in a movement-constrained condition, where their shoulders were held fixed to limit trunk tilting movements. Participants were requested to minimize head movement throughout the protocol. This protocol with a constrained reaching task condition was applied to fit with our clinical trial in stroke

Table 1
Characteristics of the participants for each group (n = 21).

Characteristics	Young group	Old group
Age (years) (SD)	25.1 (± 4.7)	73.1 (± 6.7)
Sex (female/male)	11/10	11/10
Handedness score (SD)	0.94 (± 0.14)	0.96 (± 0.08)

Groups handedness score was compared using unpaired Student t-tests; there was no significant difference.

patients (<https://clinicaltrials.gov/ct2/show/NCT04291573>) to determine the effects of trunk compensation. In the current study, since there were no significant differences between reaching task conditions for either healthy group, only the results of the free movement condition are reported.

2.3.2. Circular steering task

Participants were seated on a chair in front of a graphic tablet (A3 size; Wacom, Kazo, Japan) with a stylus moulded onto a mouse pad. The task consisted in a circular steering task based on the speed-accuracy trade-off [37]. The task was delivered on the computer using a lab-made software, the LSL-Mouse (<https://github.com/KarimaBak/LSL-Mouse>). The software displayed on a 24-inch screen a circular target (33-inch circumference) with a 2 cm tunnel in which the participants had to move a cursor as fast as possible in a clock-wise direction during blocks of 20 s. Blocks of training were done in order to familiarize with the task requirement providing verbal encouragement to focus on the speed of the task. Participants had to speed up if errors (any time outside the 2 cm circle tunnel boundaries) were less than 15% (based on pilot testing) during the training. During the experimental task, no more instructions were given. The task then consisted on 3 blocks for each arm (20 s of task with 20 s of rest). Participants started first with their non-dominant hand.

2.4. Brain activity

During the whole session, participants were equipped by a customized EEG-fNIRS headcap with an inter-optode distance of ~3 cm allowing to record the left and right sensorimotor cortical regions during the 2 functional motor tasks (see Fig. 1). EEG and fNIRS signals were simultaneously measured using a wireless Starstim fNIRS integration system (Starstim8, Neuroelectronics, Barcelona, Spain; Octamon+, Artinis Medical Systems, the Netherlands). EEG and fNIRS signals were recorded for approximately 10 min for each task. The Brodmann's areas covered by the different fNIRS channels were extracted via the NFRI function [38] from the MNI (Montreal Neurological Institute) coordinates (Table 2). Cartesian coordinates were obtained with a 3-dimensionnal digitizer (Patriot®, Polhemus Inc., USA) allowing the surface locations of the fNIRS optodes and EEG electrodes. The

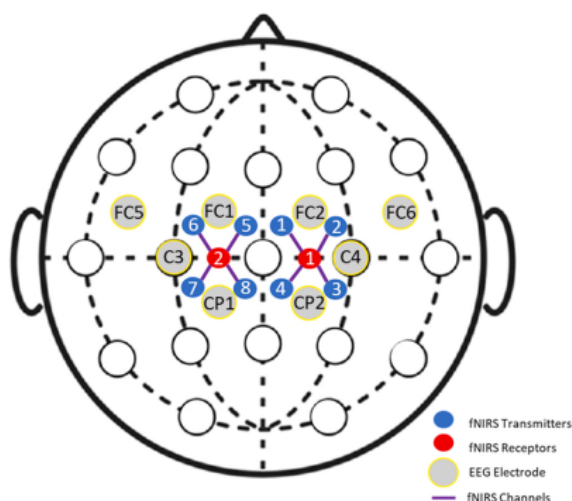


Fig. 1. Placement of the 8 fNIRS and 8 EEG channels covering the bilateral sensorimotor cortices represented on the international 10–10 EEG system layout (see Table 1 for MNI locations). In grey, the 8 EEG electrodes. For the fNIRS layout, the blue circles are the 8 transmitters and the red circle are the 2 receivers (1: right hemisphere; 2: left hemisphere).

Table 2

Locations of fNIRS probes and EEG electrodes over the sensorimotor cortices. On the left, combination receiver (Rx) and transmitter (T) label for the probes and selected electrodes of the international 10–10 EEG system. On the middle, MNI coordinates for each fNIRS and EEG channel (n = 16) with x, y, and z coordinates. On the right, Brodmann area (BA) correspondence (number, name and %) extracted from the NFRI function. R and L are for right and left hemispheres, respectively.

fNIRS EEG Characteristics	MNI coordinates			BA
	X	Y	Z	
fNIRS – Rx1-Tx1 R	26	-5	90	6, 4
fNIRS – Rx1-Tx2 R	45	-9	81	6, 4
fNIRS – Rx1-Tx3 R	44	-27	85	4, 6, 3, 1
fNIRS – Rx1-Tx4 R	24	-23	94	4, 6, 3
fNIRS – Rx2-Tx5 L	-24	-3	90	6, 4
fNIRS – Rx2-Tx6 L	-48	-7	79	6, 4
fNIRS – Rx2-Tx7 L	-43	-24	87	4, 6, 3, 1
fNIRS – Rx2-Tx8 L	-24	-20	94	4, 6, 3
EEG – C4 R	58	-18	72	6, 3, 2, 1
EEG – FC2 R	24	27	77	6, 8
EEG – FC6 R	69	14	38	6, 9
EEG – CP2 R	26	-48	93	7, 5, 3, 4
EEG – C3 L	-62	-25	71	4, 2, 1
EEG – FC1 L	-38	-1	83	6, 4
EEG – FC5 L	-76	-13	46	6, 2, 1
EEG – CP1 L	-31	-65	86	7, 5

BA: 1,2,3 (primary somatosensory cortex); 4 (primary motor cortex); 5 (somatosensory association cortex); 6 (premotor and supplementary motor cortex); 7 (parietal cortex); 8 (frontal eye-field); 9 (frontal cortex).

positioning of the 16 channels constituted 4 NIRS and 4 EEG channels per hemisphere. The arrangement is presented on Fig. 1. After being equipped, participants were asked to perform a wrist extension task to check if the movement produced was inducing a hemodynamic response.

2.4.1. Electroencephalography – EEG

The EEG used was an 8-channels design. Electrodes were located on and around SM1 cortices: right hemisphere (C4, FC2, FC6, CP2) and left hemisphere (C3, FC1, FC3, CP1) according to the international 10–10 EEG system. The electrodes (NG Gelrode, Neuroelectronics) were filled up with electro-gel (Signa Gel®). Reference electrodes (CMS, DRL) were placed over the right earlobe using an earclip. The EEG spectrum was sampled at 500 Hz. The EEG device was connected using WIFI and controlled by the computer through a software interface (Neuroelectronics Instrument Controller, NIC v 2.0).

2.4.2. Functional near infrared spectroscopy – fNIRS

A continuous-wave fNIRS system using two wavelengths was used for measuring the changes in HbO₂ and HbR overlying the left and right SM1 at a sampling frequency of 10 Hz. The optodes (2 receivers -light-detection probe- and 8 transmitters -light-emission probe- resulting in a total of 4 channels per hemisphere, Fig. 1) were placed securely on the participant's head using a fit neoprene cap to get a stable optical contact with the scalp by generating an equal amount of pressure. The two receivers were placed on C1 and C2 locations of the 10–10 EEG system. The respective four transmitters were located at a distance of 3 cm from the receivers thanks to plastic holders. The fNIRS device was connected using Bluetooth and controlled through a software interface (Oxysoft, v 3.2.51.4).

2.5. Data analysis

2.5.1. Task performance

For the reaching task, the analysis of UL reaching kinematics was allowed by an LSL-Kinect software (LSL-KinectV2: <https://github.com/KarimaBak/LSL-KinectV2>; [39,40]). All the participants correctly reached the target and the mean peak of velocity of the hand to reach the

ball (mm/s) was computed. For the kinematics analysis, 5 participants during Kinect recording of the paced reaching task, were unusable.

For the circular steering task, in order to quantify the speed-accuracy trade-off, an index of effective performance (Ipe, [41]) was calculated. Ipe (bits/s) was defined as function of an index of effective task difficulty (Ide): $Ide = \frac{2\pi Re}{Wc}$, with Ide in bits, Re the mean radius of the circular drawing and We the effective target width path $We = 4.133 * \sigma$, [42] where σ is the standard-deviation of the radius; $Ipe = \frac{Ide}{MT}$, with Ipe in bits/s, and MT, movement time in seconds. The speed (number of laps per seconds) and accuracy (percentage spent inside the 2 m tunnel) of the movement were also computed. For each participant and each arm, the median of the 3 blocks for each parameter was assessed.

2.5.2. Brain activity (fNIRS and EEG)

All fNIRS raw data analysis was undertaken using HOMER toolbox on MATLAB (Homer2 NIRS processing package, [43]) using the generated files of the Lab Recorder (xdf files). Following previously used pipeline [44], optical density time series were first converted into relative concentrations of HbO₂ and HbR using the modified Beer-Lambert law corrected by a differential pathlength factor depending on the age of the participant ([45], function hmrOD2Conc of Homer2). All data were band-pass filtered (Low cutoff: 0.08- high cutoff: 0.009 Hz; function hmrBandpassFilt of Homer2) to eliminate physiological confounds such as low-frequency drift, Mayer-wave systemic oscillations, breathing rate and heart rate components [46]. Onset of each movement and rest periods were then identified on the fNIRS signals. Motion artifacts were visually checked and removed manually when a sudden change of HbO₂ and HbR traces were observed. The corresponding epoch was then excluded. With visual rejection and outliers' detection, 14% of the fNIRS signals were rejected for the Young group, and 8% for the Older group. Each block of 5 movements was then corrected with a zero-baseline value based of the onset of the first movement. The relative concentration changes of HbO₂ and HbR were computed within the motor task intervals (0–20 s) to reflect the immediate hemodynamic response [47]. After having verified the neuro-vascular coupling occurrence during functional movement (i.e., rapid increase in HbO₂ with a lower-amplitude reduction or flat signals in HbR), the value and latency of the larger variation (peak), the average and the area under the curve values were computed for each block of 20 s, each participant and for each haemoglobin species. Given the findings were similar among the three measures of magnitude (peak, average and area under the curve), and that HbO₂ is most sensitive for motor task-related hemodynamic changes, the relative changes in peak HbO₂ concentration were employed as the indicator of brain activity; the time to peak HbO₂ concentration is also presented. These parameters were averaged by tasks (paced reaching; circular steering) and hand condition (dominant; non-dominant).

All EEG data analysis was undertaken using EEGLAB toolbox on MATLAB ([48], version 2021.1) using the generated files of the Lab Recorder (xdf files). First, data were converted from nanovolts to microvolts and re-referencing with the channel-average method and the signal was resampled at 250 Hz. It was then filtered using a band-pass filter between 0.3 and 50 Hz. Due to EEG-device troubles during acquisition, 4 participants of the Older group on the reaching task and 2 on the circular steering task were excluded. All signals were manually reviewed, those affected by noisy channels, noisy trials, and trials with abnormal movement were rejected. With visual inspection and outliers' detection, for the Young group, 2% of the signals were rejected and 6% for the Older group. Onset of each movement and rest periods were then detected on the signal. The event-related spectral perturbations (ERSP) in the alpha (8–13 Hz) and beta (14–29 Hz) rhythms were calculated as a visualisation of the average power changes in these specific time-frequencies. They provide details about the event-related desynchronization (ERD; percentage of power decrease in a specific frequency band relative to the baseline – i.e., rest) and synchronisation

(ERS; percentage of power increase in a specific frequency band relative to the task). A baseline correction was applied by subtracting the mean power changes in a 1 s baseline period from each spectral estimation, to normalize the ERS.

To quantitatively evaluate the ERS patterns for the different UL motor tasks, the relative power using the instantaneous power spectrum (Pn), the mean power spectra (Prest) during the rest period (Trest) and the mean power spectra (Ptask) during the task period (Ttask) were computed as follows [26]:

$$Prest = \frac{1}{|Trest|} \sum_{n \in Trest} Pn,$$

$$Ptask = \frac{1}{|Ttask|} \sum_{n \in Ttask} Pn,$$

$$RP(n) = \frac{Pn - Prest}{Prest} \times 100$$

$$RP = \frac{Ptask - Prest}{Prest} \times 100$$

Mean ERSs were calculated and averaged by tasks (paced reaching and circular steering) and hand conditions (dominant and non-dominant) during rest and movement periods.

$$RP = \frac{Prest - Ptask}{Ptask} \times 100$$

2.6. Statistical analyses

Statistical analyses were performed using R version 3.6.1 and RStudio version 2022.07.06. Parametric tests were used as the data were normally distributed after using the Shapiro-Wilk test and by creating Q-Q plots. Effect sizes were reported with the partial eta square (η^2_p) for the effects of the ANOVAs [49], considering a small (0.02), medium (0.13) and large (0.26) effect [50]. Statistical significance was set at $p < .05$. Significant observations were interpreted when $\eta^2_p > .02$. All values are reported mean (SD) unless specified otherwise. No three-level interaction effects were found, so only two-level interaction effects were reported with each factor combinations. For significant interactions, post-hoc Tukey comparisons were performed. Note that degrees of freedom of the analysis are different as there were not always the same number of subjects excluded for the different variables.

A mixed ANOVA with age (young and old) as a between-subject factor, and hand (dominant and non-dominant hand) as within-subject factors was performed on the movement parameters (circular steering task: Ipe, speed and accuracy; paced reaching task: velocity peak).

A mixed ANOVA with age (young and old) as a between-subject factor, and hand (dominant and non-dominant hand) and hemisphere (ipsilateral and contralateral to the movement) as within-subject factors was performed on the fNIRS Δ HbO₂ parameters (peak, time to peak) and on the EEG Alpha and Beta ESRPs.

In order to explore the relationship between performance of circular steering task and brain activation (fNIRS peak Δ HbO₂) according to the age groups, an efficiency ratio (eR = (Performance - brain activation) / (Performance + brain activation) * 100) was calculated. An independent t-test with Age (young and old) as factor was performed on eR. Finally, a spearman rank correlation analysis was applied for both age groups independently between motor performance indices of the circular steering task and brain activation parameters.

3. Results

3.1. Tasks performance (Fig. 2)

On the paced reaching task, there was no Age effect ($F_{(1,35)} = 0.027$, $p = .871$, $\eta^2_p = .00$) or Age x Hand interaction ($F_{(1,35)} = 1.71$, $p = .199$,

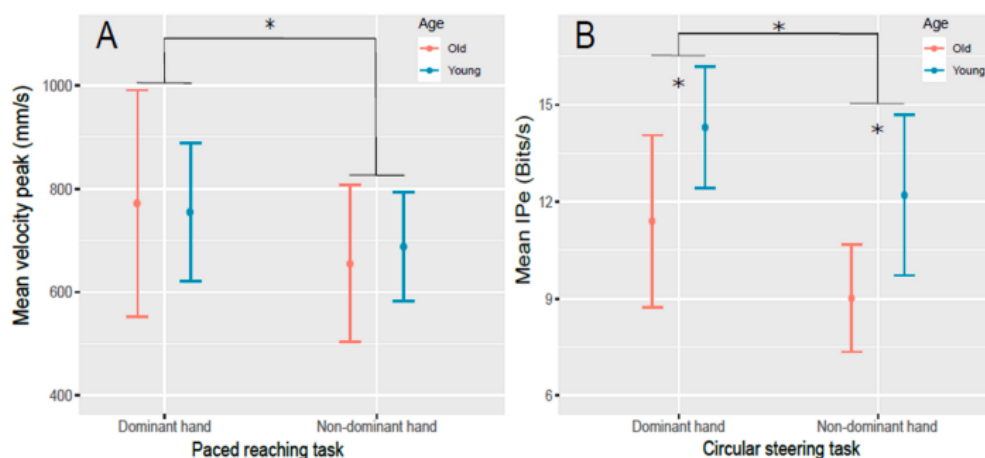


Fig. 2. Upper limb motor task performances (mean \pm SD) for the two age groups and according to the hand dominance. A) Velocity peak differences for hand dominance on the paced reaching task, B) Index of performance (IPe) differences on the circular steering task for the young and older groups and hand dominance (* for statistically significant differences at $p < .05$).

$\eta^2_p = .05$). Nevertheless, we found that for both groups the mean velocity peak was higher with the dominant hand than with the non-dominant one (Hand: $F_{(1,35)} = 23.59, p = .000, \eta^2_p = .40$).

We found a higher performance (IPe) in the young group and with the dominant hand (Age: $F_{(1,40)} = 26.79, p = .000, \eta^2_p = .40$; Hand: $F_{(1,40)} = 45.87, p = .000, \eta^2_p = .53$) with no Age \times Hand interaction ($F_{(1,40)} = 0.19, p = .664, \eta^2_p = .00$). For the speed component, we found higher values in the young group and with the dominant hand (Age: $F_{(1,37)} = 6.71, p = .014, \eta^2_p = .15$; Hand: $F_{(1,37)} = 25.55, p = .000, \eta^2_p = .41$), but no Age \times Hand interaction ($F_{(1,37)} = 0.41, p = .521, \eta^2_p = .01$). For the accuracy component, we did not find any significant main or interaction effects (Age: $F_{(1,40)} = 2.23, p = .136, \eta^2_p = .06$; Hand: $F_{(1,40)} = 1.17, p = .29, \eta^2_p = .03$; Age \times Hand interaction: $F_{(1,40)} = 0.06, p = .813, \eta^2_p = .00$).

3.2. Brain activity

Brain activity (fNIRS: peak of ΔHbO_2 and time to peak; EEG: ERD and ERS) during paced reaching and circular steering tasks are presented in Fig. 3 (fNIRS) and Fig. 4 (EEG) and the statistical results are detailed in Table 3.

The analysis of the mean ΔHbO_2 peak on the paced reaching task showed there was no main effect of Age. The Hand \times Hemisphere interaction (complemented with Tukey's post-hoc mean comparisons) revealed a higher activation in the contralateral side compared to the ipsilateral one, but only when the task was performed with the non-dominant hand. On the same task, the analysis of the time to peak ΔHbO_2 showed a significant Age \times Hemisphere interaction. Tukey's post-hoc mean comparisons revealed that for the older group, there was a Hemisphere effect with a longer time to peak ΔHbO_2 in the contralateral than ipsilateral side.

The analysis of the mean ΔHbO_2 peak on the circular steering task

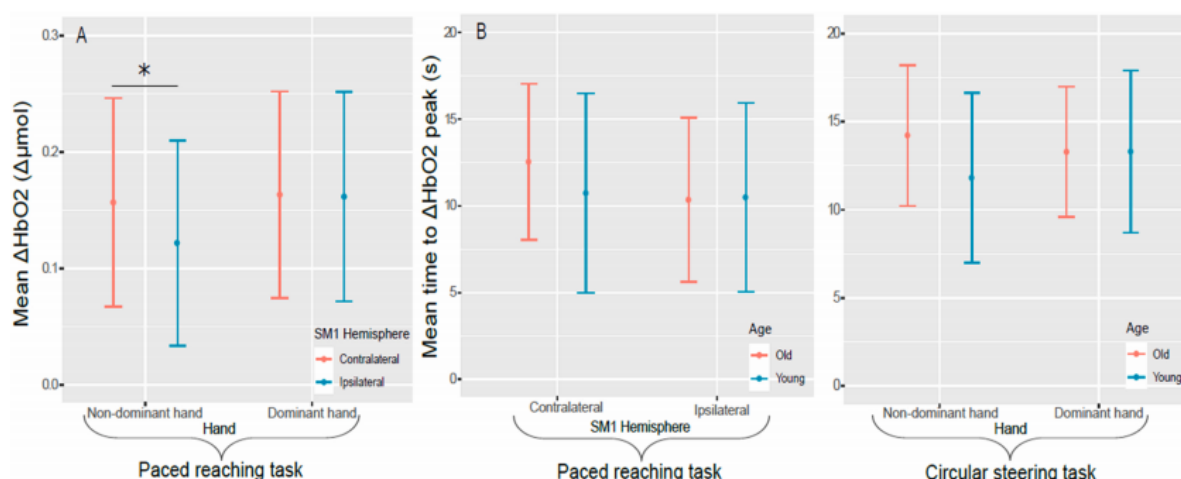


Fig. 3. fNIRS main results. A) fNIRS-derived mean (\pm SD) ΔHbO_2 peak in the contralateral (red) and ipsilateral (blue) sensorimotor (SM1) hemisphere during paced reaching task as a function of hand used (no significant Age effects, only a Hand \times hemisphere interaction, * $p < .05$, see Table 3). B) fNIRS-derived mean (\pm SD) time to peak ΔHbO_2 for old (red) and young (blue) age group as a function of SM1 hemisphere (paced reaching task Age \times Hemisphere interaction) or hand used (circular steering task Age \times Hand interaction).

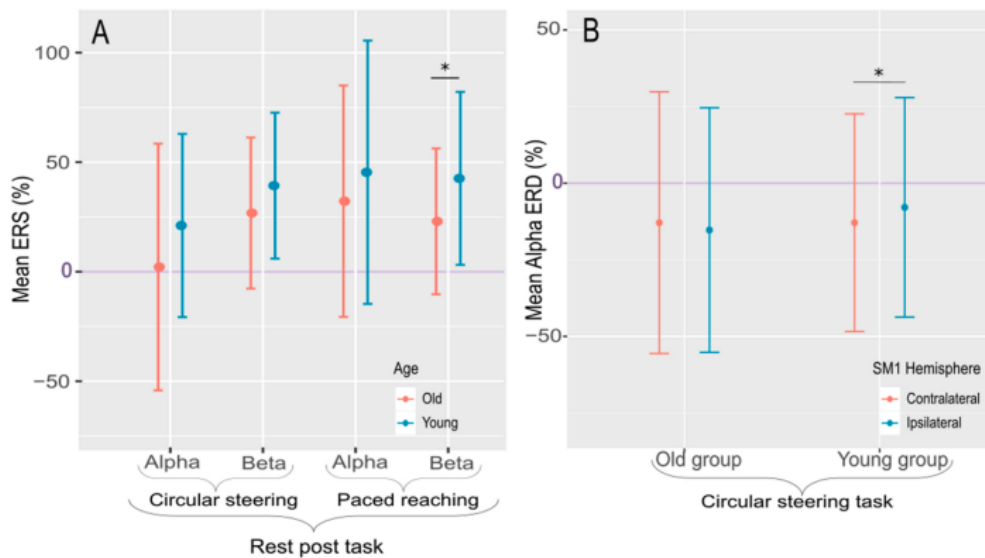


Fig. 4. EEG main results. A) Mean (\pm SD) event related synchronization (ERS) in Alpha (8–13 Hz) and Beta (14–29 Hz) power during the post task resting periods. B) Mean (\pm SD) event related desynchronization (ERD) in Alpha power for the contralateral (in red) and ipsilateral (in blue) sensorimotor (SM1) hemispheres during the circular steering task. (* for statistically significant difference at $p < .05$, see Table 3).

showed there were no main effects of Age, Hemisphere, or Hand nor any Interactions. The analysis of the time to peak Δ HbO₂ showed an Age x Hand interaction. Post-hoc comparison revealed that the time to peak for the dominant hand, in comparison to the non-dominant one, was

shorter for the young group and longer for the older group.

The analysis of the mean ERS on the paced reaching task showed a main effect of Age on the Beta ERS with a higher post movement synchronisation of the younger group. No Age Hand, Hemisphere or

Table 3

Statistical results of the ANOVA on the EEG and fNIRS brain parameters for the paced reaching and circular steering tasks.

	A.	AGE	HEMISPHERE	HAND
	<i>EEG</i>			
Paced reaching task	Alpha ERD	$F_{(1,34)} = 2.09, p = .158, \eta^2_p = .06$	$F_{(1,34)} = 0.03, p = .871, \eta^2_p = .00$	$F_{(1,34)} = 0.82, p = .371, \eta^2_p = .02$
	Beta ERD	$F_{(1,34)} = 0.52, p = .476, \eta^2_p = .02$	$F_{(1,34)} = 0.30, p = .586, \eta^2_p = .01$	$F_{(1,34)} = 0.77, p = .767, \eta^2_p = .00$
	Alpha ERS	$F_{(1,33)} = 2.50, p = .123, \eta^2_p = .07$	$F_{(1,33)} = 0.39, p = .538, \eta^2_p = .01$	$F_{(1,33)} = 1.69, p = .203, \eta^2_p = .05$
	Beta ERS	$F_{(1,29)} = 4.60, p = .041, \eta^2_p = .14$	$F_{(1,29)} = 1.62, p = .213, \eta^2_p = .05$	$F_{(1,29)} = 0.37, p = .549, \eta^2_p = .01$
	<i>fNIRS</i>			
	Δ HbO ₂ peak	$F_{(1,35)} = 0.94, p = .338, \eta^2_p = .03$	$F_{(1,35)} = 20.88, p = .000, \eta^2_p = .37$	$F_{(1,35)} = 1.05, p = .313, \eta^2_p = .03$
	Time to peak	$F_{(1,38)} = 2.99, p = .092, \eta^2_p = .07$	$F_{(1,38)} = 18.56, p = .000, \eta^2_p = .33$	$F_{(1,38)} = 2.01, p = .164, \eta^2_p = .05$
	<i>EEG</i>			
Circular steering task	Alpha ERD	$F_{(1,31)} = 0.18, p = .672, \eta^2_p = .01$	$F_{(1,31)} = 0.41, p = .526, \eta^2_p = .01$	$F_{(1,31)} = 0.94, p = .341, \eta^2_p = .03$
	Beta ERD	$F_{(1,31)} = 0.43, p = .517, \eta^2_p = .01$	$F_{(1,31)} = 0.04, p = .838, \eta^2_p = .00$	$F_{(1,31)} = 0.24, p = .625, \eta^2_p = .01$
	Alpha ERS	$F_{(1,33)} = 4.10, p = .051, \eta^2_p = .11$	$F_{(1,33)} = 0.02, p = .882, \eta^2_p = .00$	$F_{(1,33)} = 7.00, p = .012, \eta^2_p = .18$
	Beta ERS	$F_{(1,33)} = 2.44, p = .128, \eta^2_p = .07$	$F_{(1,33)} = 1.98, p = .169, \eta^2_p = .06$	$F_{(1,33)} = 4.88, p = .034, \eta^2_p = .13$
	<i>fNIRS</i>			
	Δ HbO ₂ peak	$F_{(1,34)} = 0.00, p = .995, \eta^2_p = .00$	$F_{(1,34)} = 0.08, p = .774, \eta^2_p = .00$	$F_{(1,34)} = 0.36, p = .552, \eta^2_p = .01$
	Time to peak	$F_{(1,37)} = 1.42, p = .242, \eta^2_p = .03$	$F_{(1,37)} = 1.47, p = .233, \eta^2_p = .03$	$F_{(1,37)} = 0.17, p = .683, \eta^2_p = .00$
	B.			
	AGE x HEMISPHERE		AGE x HAND	
	<i>EEG</i>			
Paced reaching task	Alpha ERD	$F_{(1,34)} = 0.76, p = .391, \eta^2_p = .02$	$F_{(1,34)} = 0.11, p = .742, \eta^2_p = .00$	$F_{(1,34)} = 0.91, p = .346, \eta^2_p = .03$
	Beta ERD	$F_{(1,34)} = 3.99, p = .054, \eta^2_p = .11$	$F_{(1,34)} = 0.00, p = .963, \eta^2_p = .00$	$F_{(1,34)} = 0.00, p = .982, \eta^2_p = .00$
	Alpha ERS	$F_{(1,33)} = 0.81, p = .376, \eta^2_p = .02$	$F_{(1,33)} = 1.11, p = .299, \eta^2_p = .03$	$F_{(1,33)} = 0.44, p = .510, \eta^2_p = .01$
	Beta ERS	$F_{(1,29)} = 0.92, p = .346, \eta^2_p = .03$	$F_{(1,29)} = 0.12, p = .727, \eta^2_p = .00$	$F_{(1,29)} = 3.57, p = .069, \eta^2_p = .11$
	<i>fNIRS</i>			
	Δ HbO ₂ peak	$F_{(1,35)} = 0.04, p = .849, \eta^2_p = .00$	$F_{(1,35)} = 0.01, p = .919, \eta^2_p = .00$	$F_{(1,35)} = 9.78, p = .004, \eta^2_p = .22$
	Time to peak	$F_{(1,38)} = 8.95, p = .005, \eta^2_p = .19$	$F_{(1,38)} = 0.00, p = .948, \eta^2_p = .00$	$F_{(1,38)} = 0.04, p = .847, \eta^2_p = .00$
	<i>EEG</i>			
Circular steering task	Alpha ERD	$F_{(1,31)} = 7.25, p = .011, \eta^2_p = .18$	$F_{(1,31)} = 0.26, p = .617, \eta^2_p = .01$	$F_{(1,31)} = 1.21, p = .279, \eta^2_p = .04$
	Beta ERD	$F_{(1,31)} = 0.33, p = .570, \eta^2_p = .01$	$F_{(1,31)} = 0.73, p = .399, \eta^2_p = .02$	$F_{(1,31)} = 0.02, p = .879, \eta^2_p = .00$
	Alpha ERS	$F_{(1,33)} = 0.01, p = .945, \eta^2_p = .00$	$F_{(1,33)} = 0.00, p = .983, \eta^2_p = .00$	$F_{(1,33)} = 0.00, p = .978, \eta^2_p = .00$
	Beta ERS	$F_{(1,33)} = 0.85, p = .364, \eta^2_p = .03$	$F_{(1,33)} = 0.06, p = .814, \eta^2_p = .00$	$F_{(1,33)} = 0.69, p = .412, \eta^2_p = .02$
	<i>fNIRS</i>			
	Δ HbO ₂ peak	$F_{(1,34)} = 0.00, p = .984, \eta^2_p = .00$	$F_{(1,34)} = 0.00, p = .997, \eta^2_p = .00$	$F_{(1,34)} = 3.13, p = .086, \eta^2_p = .08$
	Time to peak	$F_{(1,37)} = 0.01, p = .928, \eta^2_p = .00$	$F_{(1,37)} = 5.66, p = .023, \eta^2_p = .13$	$F_{(1,37)} = 1.29, p = .263, \eta^2_p = .03$

A. Effects of AGE (Young vs Old), Hemisphere (Contralateral vs Ipsilateral) and Hand (Dominant vs Non-dominant) on the Alpha and Beta ERS. B. Two-levels interaction of the model. In bold, results with $p < .05$ and $\eta^2_p > .02$.

Interaction effect were found on the other EEG dependant variables (Alpha ERS, Alpha ERD, Beta ERD, see Table 3).

The analysis of the mean ERSP on the circular steering task showed no main effect of Age on the Beta and Alpha power modifications. However, there was an Age x Hemisphere interaction on the Alpha ERD. Post-hoc comparisons showed that Alpha ERD was significantly greater in the contralateral than ipsilateral sensorimotor area for the young group ($p = .012$), with no significant differences between hemispheres for the older group ($p = .197$). The results also showed a main effect of the Hand on the Alpha and Beta ERS, with a higher synchronisation after movements with the dominant than non-dominant hand.

Finally, looking at the difference between the changes in brain activity (fNIRS peak O2Hb) and circular task performance (Ipe), we found that the eR was greater for the young group in comparison to the older group ($F_{(1,37)} = 5.48$, $p < .05$, $\eta^2_p = .034$). Moreover, we found a positive correlation between the accuracy component of the circular steering task and the level of activation in fNIRS for both groups (ipsilateral: $p < .05$, $\rho = .29$; contralateral: $p < .05$, $\rho = .26$). Nevertheless, we did not find any correlation between the movement parameters and the ERD-ERS.

4. Discussion

This study is the first to investigate the age-related changes in the hemodynamic and electrical responses of the ipsilateral and contralateral sensorimotor areas in relation to unilateral proximal UL motor performance. For that purpose, we recorded the brain and the UL movements synchronously using combined fNIRS/EEG neuroimaging and kinematics methods. Two functional proximal UL tasks encountered in daily life were explored: a paced reaching target task and a circular steering task to capture the speed-accuracy trade-off. The primary aim was to determine potential hemispheric and hand dominance differences of the brain hemodynamic (fNIRS) and electrical (EEG) activity during proximal UL motor tasks with physiological aging. The fNIRS time course analysis (time to peak ΔHbO_2) showed aging effects on the rate of the neurovascular coupling response in the bilateral SM1 during both proximal UL tasks depending on the hemisphere and on the hand used. The Alpha ERD showed a greater contralateral to ipsilateral Alpha ERD for the young group in the circular steering task. Moreover, aging led to smaller power in the Beta ERS of the paced-reaching task; a similar trend was observed for Alpha ERS for circular steering task. The secondary aim was to explore the effect of aging on the relationship between motor performance and brain related activity in order to characterise the neural efficiency of movement. Looking to the relationship between brain pattern and motor performance, even though the fNIRS peak HbO_2 and EEG Alpha and Beta ERD were similar between age groups during the circular steering task, performance (Ipe and speed) and efficiency ratio ($eR = \text{Ipe}/\text{Peak } \Delta\text{HbO}_2$) were lower in the older group.

Altogether, our study showed some age-related differences in fNIRS and EEG parameters. On the paced reaching task, with similar fNIRS amplitude and performance, we found that with physiological aging there was a delayed time to peak ΔHbO_2 amplitude in the contralateral than ipsilateral hemisphere. On the circular steering task, we found a delayed time to peak ΔHbO_2 amplitude in the bilateral sensorimotor network when the task was performed with the non-dominant hand but not with the dominant hand. These results can be explained by a reduction of the speed of increase in cerebral blood flow following a neural activation causing an impaired neurovascular coupling response [51]. In addition, the results provided by EEG Alpha ERD suggest an aging related modification of excitatory-inhibitory capacity in the bilateral sensorimotor network, such that while the young group showed a greater Alpha ERD in the contralateral than ipsilateral hemisphere, the older subjects required similar levels of Alpha ERD in the bilateral sensorimotor network. This suggests that a greater excitatory capacity (Alpha ERD) was necessary from the ipsilateral sensorimotor network

for the older group to achieve this circular steering task performance. This could be explained by the reduction of interhemispheric inhibition present in older adults that is leading to an increase bilateral activity [52]. Moreover, older subjects presented a lower Beta (paced reaching) and Alpha ERS (trend for the circular steering, $p = 0.051$ and $\eta^2_p = .11$) traducing a reduced ability to disengage the activated neural circuits at the end of the tasks. Looking to the literature around the effect of aging, the ERS analysis is presenting contrasting results. Some teams showed a reduced ERS with aging [30] when others did not observe effects of aging on the magnitude of ERS [31]. Our results on EEG are thus, giving complementary results to the already existing contrasting literature of aging. Finally, this potential age-related decrease in ERS could be a key EEG parameter to understand the performance reduction on the circular steering task.

Overall, these novel findings suggest that physiological aging might reduce the neural efficiency to perform functional proximal UL movements, particularly when performance (speed-accuracy) needs to be taken into consideration. Herein, older participants showed a reduced motor performance and efficiency ratio. In addition, the older group had a slower neurovascular coupling response (i.e., a longer fNIRS time to peak ΔHbO_2) and reduced ability to disengage (inhibit) movement related neural circuits (i.e., EEG ERS) in the bilateral sensorimotor areas. These age-related modifications in bilateral sensorimotor network activation coupled with lower performance (circular steering task: Ipe, Speed) and efficiency ratio (eR), could suggest that the ability to efficiently recruit the bilateral sensorimotor network to perform the proximal UL tasks was lower for the old group compared to the young group.

Regarding our main fNIRS outcome, we did not find any Age x Hemisphere effect on both tasks and difference in the level of activation. Our results differ from previous studies that have highlighted aging-related differences in asymmetry of brain activity in distal UL tasks and dual tasks, such as dual-task walking and hand motor tasks with greater dexterity [4,16], and most notably during purely cognitive tasks requiring executive function [15]. Nevertheless, we did find an age x hemisphere effect with the EEG. Knowing the ability of the EEG to differentiate the excitatory state to the inhibitory one, we can hypothesize that in this task, to reach the higher performance required, the older subjects were over-activating their bilateral SM1. It is nevertheless really complicated to compare our results to previous studies, because none has looked to the Age x Hemisphere interaction during proximal UL movements. An explanation to this difference of age effect could also be in the area covered. Possibly, as the motor network involved in motor action is including more brain areas with aging, the controversial results in the literature could be explained by the brain areas explored [53]. For instance, as the circular steering task is involving a cognitive control, it could have been interesting to look to the parietal and frontal areas [54]. However, since our fNIRS-EEG measurement zone did not extend to more upstream motor control centres in the prefrontal cortex, any increases in the amplitude and/or area of activation to compensate for the reduced inhibitory capacity of the sensorimotor network during resting periods in older adults could not be verified. Although previous studies have confirmed such an extended prefrontal activation pattern to compensate for inefficient neural processing in sensorimotor circuits in older population [17,55], future studies with a more extended prefrontal region measurement should be undertaken to confirm such a mechanism in our experimental protocol.

Looking to the specific brain pattern of the tasks, we found that peak ΔHbO_2 and EEG ERD/ERS parameters on the two unilateral proximal UL movements evaluated showed a relative bilateral SM1 activation for most of the task conditions. This could be an explanation for the absence of aging effect on the asymmetry of SM1 activation as the younger subjects already yield, on these tasks, a bilateral SM1 activation for most of the conditions. The more proximal nature of the UL movement (mainly involving the elbow and shoulder joints) to perform the paced reaching and circular steering tasks already reduces any asymmetry of lateralised sensorimotor network activation because the elbow and

shoulder joints classically involve more ipsilateral activations than distal movements [24].

For the paced reaching task there were no overt difficulty constraints, and in the literature the modification of brain activation for motor control in aging is linked to the evolution of performances [14, 56]. Moreover, studies that have looked to the brain asymmetry evolution with aging on reaching tasks used a speed component for the movement [4,20]. However, our reaching task was paced with a 2 s period to reach the target and 2 s of rest back to the sitting position. Regarding the similar strategy used by all participants (i.e., faster with the dominant hand), a similar more bilateral activation pattern was required for both groups, which can explain the absence of further asymmetry reduction of brain activation in the older population.

The second movement explored, the circular steering task has a higher speed-accuracy movement control, which can explain the bi-hemispheric sensorimotor network activation of both populations. This absence of brain asymmetry could be due to the type of strategy used to perform the task. It has been shown on more distal UL tasks that complex movements are organized more bilaterally in the sensorimotor areas, particularly the primary and premotor areas [9]. Furthermore, the speed during this circular steering task was not controlled but biased to focus on the speed while maintaining constant a level of accuracy. It is indicated in the literature that with an increased speed, there is an increased ipsilateral activation to support the contralateral hemisphere [57]. The poorer performance on a speed-accurate proximal movement is in accordance with literature saying that there was a decline in manual dexterity in old age and that the time to accomplish a task was increasing [58].

Looking to the association of fNIRS and EEG for investigation of functional task motor control seems promising. These two methods are considered as standard in the field of functional neuroimaging. Measurements obtained from each of these two modalities provide complementary information related to functional activity of the brain. With a high temporal resolution, EEG can detect electrophysiological that span different frequency band and can occur simultaneously of in succession. For the fNIRS, the temporal indecision is not allowing such differentiation of electrophysiological signatures with for instance no differentiation between inhibitory and excitatory synaptic activity [59, 60]. Reversely, the EEG is recording responses of more widespread areas that could lead to spatial differentiation difficulties [24]. With our result, we reinforce the interest for the integration of these two methods for monitoring of brain hemodynamic and electrical activity in several healthy and pathological population for a variety of tasks (see [61] for a review).

This study presents a few methodological limitations. First, due to an EEG device issue, fewer old subjects were included in the final EEG data set. This could have led to false effects, or reversely to effects that could not be identified with fewer data, which could be the case with the close to our significance cut off found for the circular steering task Alpha ERS ($p = 0.051$). Regarding the inclusion criteria, the older subjects recruited in this study were physically active, thus, it could have an influence on the brain responses and physical performances that were close to the young group. In further research it would be relevant to look if there is specific brain reorganization when the motor performances are more or less affected by aging [15,62]. We did not apply systemic physiology artifact correction for fNIRS signals by means of a short distance channel regression procedure. We adopted in the present study the following approaches when defining the experimental setup to minimize false positives. The study protocol was designed for inducing important contrast between the functional motor task and the resting period, employed UL movements on a horizontal plane below the level of the shoulders and heart for avoiding large blood pressure changes affecting HbO₂ and HbR concentrations, and used adequate pressure provided by the headcap to induce a partial transient blockage of the skin circulation during the fNIRS study [63] as witnessed by the presence of the well-defined circles over the skin that disappears about

15 min after the test session. Further investigations are needed to confirm our first findings by using simultaneous recording from deep- and shallow-separation optodes.

5. Conclusion

This study using combined fNIRS-EEG results showed that during real-world functional UL tasks involving proximal arm joint movements (shoulder and elbow), the bi-hemispheric sensorimotor network activation pattern seen in the young group was not affected by aging. For the circular steering task that had a speed-accuracy constraint, although it appears that healthy aging brain activity was at similar levels as their younger counterparts, the global performance was lower, suggesting a reduced neural efficiency. Indeed, EEG results showed that aging affected synchronization of the post task-related bilateral sensorimotor brain rhythms (Beta ERS) and increased ipsilateral desynchronization (Alpha ERD) for the circular steering task. We demonstrated the interest of using two types of UL tasks when monitoring brain activity, a task that is discrete with loose time-accuracy constraint (paced reaching) and another task which is continuous with high speed-accuracy constraints (circular steering). These proximal UL tasks can have clinical translation, such that if we look at post-stroke neuro-rehabilitation, the proposed tasks could be used to evaluate the evolution of the level of brain activity and performance during functional proximal UL movements that can be performed by most post-stroke patients as compared to more distal UL movements. Since the majority of stroke survivors are also affected by aging, knowing which activation we can expect in a healthy brain of an older person could help to better observe and understand how the brain is evolving through a neuro-rehabilitation program.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CRedit authorship contribution statement

Camille O. Muller: Writing – original draft, Investigation, Analysis, Visualization, Data curation, Formal analysis. **Stéphane Perrey:** Supervision, Writing – review & editing, Conceptualization, Project administration. **Karima Bakhti:** Writing – review & editing, Conceptualization, Methodology. **Makii Muthalib:** Writing – review & editing, Conceptualization, Methodology, Data curation. **Gérard Dray:** Writing – review & editing, Analysis, Visualization, Methodology. **Binbin Xu:** Writing – review & editing, Analysis, Visualization, Methodology, Data curation. **Denis Mottet:** Writing – review & editing, Conceptualization, Methodology, Data curation. **Isabelle Laffont:** Supervision, Writing – review & editing, Conceptualization.

Declaration of Competing Interest

The authors have no conflict of interest to declare.

Data availability

Data will be made available on request.

Acknowledgement

We acknowledge ReArm project (PHRIP-2018-0731) for the use of facilities (EEG and fNIRS devices) in the completion of this work.

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7.3. Chapter key-points

HEALTHY AGING EFFECTS ON TASK-RELATED BRAIN ACTIVITY AND KINEMATICS

- **Aim** – evaluate the effect of healthy aging on the bilateral sensorimotor (SM1) activation patterns of functional proximal UL movements
- **Methods** – Combined fNIRS-EEG system was synchronized with movement capture system to record SM1 activation while moving in 21 young (mean age = 25 yrs) and 21 healthy old (mean age = 73 yrs)
- **Results** –
 - Movement strategies:
 - Decreased performance on circular steering task for the older but hand dominance preserved
 - Same strategies for both tasks
 - Brain modifications:
 - No SM1 reorganization during the reaching task
 - SM1 higher EEG ipsilateral desynchronization on the circular steering for older
 - Trend to lower post-movement synchronization for older
- **Conclusions** – identification of age-related changes in brain electrical and hemodynamic response patterns in the bilateral sensorimotor network. Greater activation in the ipsilateral hemisphere during the circular steering task (i.e., task with higher demand than reaching).

NEXT STEP

Comparison with a stroke population (i.e., high incidence in old population). Identification of supplementary brain and movement adaptation with the pathology?

Panel 8

Chapter 8: Task-related brain activity and kinematics in post-stroke patients

8.1. Context – objectives

In the previous study we suggested that with healthy aging, we had an increase in the EEG excitatory activity of the ipsilateral hemisphere, and a reduced ability to disengage the activated neural circuits at the end of the tasks. Moreover, at a kinematics point of view, we found that the elderly had a reduced performance on the circular steering task, and that this task was more sensitive to aging movement effect. The same methodology was applied in a second experimental study to answer to our third objective “the effects of pathological aging on the related brain activity of UL functional tasks”.

The aim here was to explore the task-related brain activity in stroke population looking to how, pathology, is affecting hemodynamic and electrical brain activity, and in relation to kinematics of movement. For this purpose, we led a comparison between healthy old adults and stroke adults to determine if these brain and movement markers on our functional tasks were affected by the stroke. The second objective of this study was to explore the link with clinical level of motor function as it is evaluated in clinical tests.

For this purpose, we collected the SM1 brain activity during the reaching and circular steering tasks. We included in this experimental study two groups : one healthy older (n = 21; mean age = 73.1 ± 6.7 yrs.) groups and one stroke group (n = 21; mean age = 64.4 ± 10.2 yrs.)

We hypothesized that movement with paretic arm will induce an ipsilateral over-activation in comparison with non-paretic arm and with healthy control subjects. Moreover, we hypothesized that paretic arm movement will lead to decreased performance and higher compensatory strategies.

The article based on this second experimental study will be submitted for peer-reviewing this spring; the current version of the article is presented in section 8.2. (Muller et al., in preparation).

8.2. Second experimental study

ARTICLE 3 : Muller C.O., Faity G., Muthalib M., Perrey S., Dray S., Xu B., Froger J., Mottet D., Laffont I., Delorme M., and K. Bakhti. (*In preparation*)

Brain-movement relationship in upper-limb functional tasks for chronic post-stroke patients

Abstract

After a stroke, brain activation reorganisation, movement compensatory strategies and their evolution through rehabilitation is a subject of major interest. Two non-invasive neuroimaging methods allow for recording the task-related brain activation: functional near-infrared spectroscopy (fNIRS) and electroencephalography (EEG) respectively based on haemodynamic response electrical activity. Their simultaneous use could allow a better spatiotemporal mapping of the brain activity and associated to kinematics assessments during movement it could unveil underlying mechanisms of functional upper limb (UL) recovery. This study aims to depict activation's patterns of the motor cortices using combined fNIRS-EEG and their association with the motor performance and strategies during UL functional tasks in chronic post-stroke patients. Twenty-one healthy old adults and 21 post-stroke patients were recruited and realized two standardised functional tasks of the UL: a paced-reaching task where they have to reach a target in front of them and a circular steering task where they have to displace, as fast as possible, a mouse inside a circular target projected on a screen. Simultaneously, activation of the motor cortices is recorded using fNIRS-EEG. Kinematics analyses showed a decreased performances in the circular steering task and an increased use of trunk compensation in post-stroke patients in both tasks. Brain analyses, showed over-activation on the reaching task for patients with paretic arm, associated to an increased use of trunk and a higher impairment (clinical scores). With this project we provided new insights about post-stroke brain and movement compensations and adaptations. This work opens up avenue for using such method to better understand brain-movement evolution through stroke rehabilitation.

Keywords: neuroplasticity; sensorimotor cortex; fNIRS; EEG; reaching and tracing tasks; stroke

1. Introduction

With a very high prevalence, stroke is the second leading cause of death and the first cause of acquired disability in adults in France. Regardless of the severity, strokes frequently result in physical limitations and compromised quality of life. With 80% of patients experiencing difficulty using their paretic arm in activities of daily living, hemiparesis emerges as one of the most frequent disabilities resulting from stroke (Alt Murphy et al., 2015). Concerning the prognosis of the upper limb (UL) functional recovery, only 12% of stroke patients fully regain arm functionality after six months (Kwakkel & Kollen, 2013).

Due to its prevalence, non-recovery function of the paretic UL is the main focus of management strategies beyond three months post-stroke, specifically in the sub-acute and then chronic stage (i.e., when the intensive rehabilitation is stopped, Miller et al., 2010). With difficulties to use to their paretic arm for daily activities, patients tend to exhibit non-mandatory trunk compensation (i.e., overuse of trunk flexion to the detriment of arm use), particularly evident during reaching tasks (Bakhti et al., 2017, 2018). These phenomena can lead to a learned non-use of the paretic arm (Taub et al., 2006), potentially encouraging brain reorganization (Lindberg et al., 2007) and limiting functional recovery (Lum et al., 2009). Indeed, functional motor recovery is partially attributed to plastic reorganization within the adult human brain (Calautti & Baron, 2003; Ward et al., 2003). Motor compensations could significantly impact this plastic reorganization (for a review see Jones et al., 2017). Thus, investigating how stroke itself affects neural activation during unilateral and bilateral UL activities may elucidate the underlying mechanisms of functional recovery (Lim & Eng., 2019).

Chronic stroke patients often demonstrate abnormal brain activation, exhibiting irregular activation in both the ipsi- and contralesional hemispheres during movement. A meta-analysis has reported an increase in activation of the contralesional primary motor cortex, and bilateral premotor and supplementary motor areas when using the paretic hand compared to healthy individuals (Rehme et al., 2011). Additional studies have demonstrated increased in contra- and ipsilesional activation during paretic UL movement in stroke patients compared to healthy individuals (Buma et al., 2010). These studies have highlighted a gradual evolution of the task-related brain activity toward a “normal” lateralized pattern of the primary sensorimotor cortex (SM1 ; Feydy et al., 2002; Tombaru et al., 2004). This pattern is conjectured to correlate with improvements in motor function (Chollet et al., 1991; Cramer et al., 1997). Specifically, research has indicated a link between brain reorganization (measure by functional magnetic

resonance imaging - fMRI) and functional recovery of the paretic arm during post-stroke rehabilitation (Dong et al., 2006). Finally, a review evaluating the use of fMRI as a post-stroke prognostic tool suggested that monitoring brain reorganization can enhance our understanding of stroke progression and potentially offer more accurate predictions of patient responses to treatment and rehabilitation (Gale and Pearson, 2012).

However, a significant limitation of the studies mentioned earlier lies in the incompatibility of the neuroimaging techniques employed with functional movement in ecological conditions. Consequently, the tasks performed under fMRI are not genuinely functional (e.g., thumb-finger opposition task, elbow flexion-extension in the supine position; Van Dokkum et al., 2016). Post-stroke rehabilitation tends to focus more on movements involving the entire upper limb (UL) (i.e., wrist, elbow, shoulder) in sitting or standing postures, more closely mirroring functional tasks employed in daily life (e.g., grasping a cup). Thus, assessment of brain activation during upright, unrestrained, functional tasks with alternative portable neuroimaging methods is needed.

In this context, two methods of recording brain activation allow the non-invasive collection of brain signals in an ecological environment while performing functional motor task. Firstly, the functional near infrared spectroscopy (fNIRS), which is based on indirect recording of the hemodynamic activity of the brain and relying, like fMRI, on the blood-oxygen level-dependant response, measures oxygenated (HbO₂) and deoxygenated (HbR) blood in the cerebral cortex (Obrig & Villringer, 2003). It allows brain monitoring in an upright position without physical restraint (Gramigna et al., 2017). This method has been utilized to measure sensorimotor network activation during UL movements in healthy young adults (Derosière et al., 2014), older healthy adults (Larivière et al., 2019) and stroke patients (Delorme et al., 2019; Lim & Eng, 2019). Although it has been shown in healthy adults that the contralateral brain is mainly activated during reaching tasks (Nishiyori et al., 2016), a more bilateral activation pattern can be observed as compared to distal UL movements (Nirkko et al., 2001). However, limited studies have investigated proximal UL movements, such as reaching, in the stroke population. To the best of our knowledge, only one recent study investigated the reaching task under ecological conditions with fNIRS in a stroke population (Lim & Eng., 2019). They found enhanced sensorimotor ipsilesional activation in the stroke patients despite poorer motor performance in reaching and grasping. Nevertheless, this study, did not measure movement kinematics (i.e., the involvement of trunk compensation, elbow extension, shoulder flexion, ...). Secondly, EEG, a method based on the direct recording of brain electrical activity, can

measures functional brain activity by detecting variations in electrical currents at the scalp due to local electric fields produced by neuronal activity (Olejniczak et al., 2006). In this context, event-related power's changes within oscillatory neural activities in EEG signals indicate the level of excitation and inhibition in the sensorimotor network and have been utilized to decode movement (Nakayashiki et al., 2014). These event-related power can be observable within specific frequency bands over the SM1 (alpha-mu – 8 to 13Hz and beta – 14 to 29 Hz). Power oscillations can be characterized by a decrease at movement execution (event-related desynchronization – ERD) or an increase at rest (event-related synchronization – ERS; Pfurtscheller et al., 1999). In subacute stroke patients, the magnitude of high-mu and low-beta ERD recorded from the lesioned hemisphere correlates with residual motor ability in the paretic UL (Bartur et al., 2019). Another study found that higher motor impairment was related to higher ERD in the unaffected hemisphere (Kaiser et al., 2012). More recently, motor dysfunction was proposed to be correlated to ERD during motor task execution (Chen et al., 2021). Like fNIRS, EEG could be used to explore related brain activation patterns during UL movements in stroke patients, and their association can lead to a better view of the spatio-temporal information of the brain activation patterns of SM1 over the two hemispheres (Yang et al., 2019b). Finally, we recently showed how complementing brain data with kinematic assessments of functional proximal UL tasks can help to better understand SM1 task-related activity (Muller et al., 2023).

The main objective of the present study was to investigate SM1 cortical activations during a paced reaching task and a circular steering task among people with and without stroke. We hypothesised an increased SM1 activation in the stroke cohort, particularly during the use of the paretic arm in both ipsi- and contralesional hemispheres. The secondary objectives of the present study were, first, to investigate the effect of stroke on the between brain activation patterns and motor performance, and second, to the effect of the spontaneous versus the trunk restrained reaching on brain activation patterns. We hypothesised that individuals in the stroke group would display inferior performance when using their paretic arm and that cortical activation in the lesioned hemisphere would positively correlate with task performance.

2. Material and methods

2.1. Participants

The study cohort consisted of 21 stroke patients and 21 healthy old adults. For the stroke group, the inclusion criteria were to: i) be aged between 18 and 90 years old, ii) be at more than

3 months of a first cerebrovascular accident of any aetiology (hemorrhagic or ischemic), and iii) have an UL motor impairment (FM-UE ≥ 15 , Fugl-Meyer et al., 1975). The non-inclusion criteria were to: i) have hemineglect or severe attentional problems (omission of more than 15 bells on the Bell's test; Gauthier et al., 1989), ii) have aphasia of comprehension dysfunction (Boston Diagnostic Aphasia Examination $< 4/5$; Kaplan et al., 1983), and iii) have severe cognitive dysfunction (Mini Mental State Examination-MMSE < 24 ; Kalafat et al., 2003). To be included, the healthy adults had to be aged between 60 and 90 years old (to fit with the stroke group age) and to be right-handed assessed by the Edinburgh Handedness Inventory (Oldfield, 1971). Exclusion criteria were the existence of neurological (including a history of traumatic brain injury) or motor disorders at the level of the upper limb (history of tendinous disease, arthritis, surgery). Healthy participants were recruited via local association and stroke ones were recruited at the beginning of a rehabilitation protocol (ReArm project, Clinical trial identifier : NCT04291573, 2nd March 2020).

Table 1 provides detailed participant information, including gender, age, lesioned side, laterality, and clinical scores (refer to the clinical assessments section for additional details). For the stroke group, Table 2 presents all patients' demographic data and clinical history.

In accordance with the Declaration of Helsinki, this study was approved from the French Research Ethics Committee, (Comité de Protection des Personnes-CPP SUD-EST II, N°ID-RCB: 2019-A00506-51, <http://www.cppsudest2.fr/>) for the stroke patients, and from the local Ethics Committee of the EuroMov DHM laboratory for the healthy subjects (EuroMov IRB, permit number 1912B). All participants provided informed written consent prior participation in the study.

Table 1. Characteristics of the participants for each group

Characteristics	<i>Healthy group (n = 21)</i>	<i>Stroke group (n = 21)</i>
Age (years) (SD)	73.1 (± 6.7)	64.4 (± 10.2)
Sex (female/male)	11/10	6/15
Handedness score (SD)	0.96 (± 0.08)	-
Paretic arm (right/left)	-	8/13
FM-UE	-	48.7 (± 5.9)
WMFT	-	57.3 (± 9.8)
BBT ratio	-	54.0 (± 25.1)

BBT ratio = (paretic score / non-paretic score) * 100

Table 2. Demographic information, clinical data, lesion information and clinical scores.

<i>P</i>	<i>Age</i>	<i>Gender</i>	<i>Hemisphere lesioned</i>	<i>HD before stroke</i>	<i>Paretic arm</i>	<i>FM-UE</i>	<i>Months after stroke</i>	<i>Type of lesion</i>	<i>BI</i>
1	62	M	L	R	R	45	8	H	85
2	61	M	R	R	L	55	73	Is	95
3	52	M	R	R	L	51	84	Is	90
4	63	M	L	L	R	44	88	Is	95
5	70	M	R	R	L	51	98	Is	100
6	73	F	R	R	L	53	223	H	-
7	63	F	R	R	L	27	21	Is	90
8	57	F	R	R	L	60	10	H	90
9	74	M	R	R	L	50	49	Is	85
10	37	M	R	L	L	46	32	Is	95
11	68	M	R	R	L	47	43	Is	95
12	76	M	L	R	R	41	93	H	90
13	62	F	R	R	L	45	12	Is	85
14	49	F	R	R	L	54	25	H	95
15	82	M	L	R	R	58	45	Is	100
16	72	M	L	R	R	44	4	H	90
17	66	M	L	R	R	38	9	H	95
18	73	M	L	R	R	36	9	H	25
19	71	F	L	R	R	57	18	-	95
20	62	M	R	R	L	46	3	H	-
21	60	M	R	R	L	43	9	Is	90

Abbreviations: M, male; F, female; R, right; L, left; HD, hand-dominance; BI, Barthel index; FM, Upper Limb Fugl-Meyer (score/66); Is, Ischemic; H, Hemorrhagic. The severity of the motor impairment was evaluating using the FM-UE in accordance with the motor impairment classification in clinical and research settings (Gladstone et al., 2002).

2.1. Experimental design

Each participant engaged in an hour-long session in a quiet isolated room. The participants were equipped with the fNIRS-EEG neuroimaging systems and performed two functional UL tasks while seated, a paced reaching arm task and a circular steering task. The setup permitted synchronized recording- of UL kinematics and brain activity (fNIRS and EEG) using lab streaming layer (LSL, <https://github.com/labstreaminglayer/App-LabRecorder>).

More comprehensive details about the functional motor task methodology can be found in our recent methodological paper (see Figure 5, Muller et al., 2021).

2.2. Upper-limb function

All participants performed the two functional tasks, as detailed in earlier studies (Muller et al., 2021, 2023).

2.2.1. *Paced reaching task*

Participants were seated on a chair fitted with armrests and were instructed to reach a target (a table tennis ball) placed in front of them at a height of 80 cm and a distance which facilitated the complete extension of the arm. A Kinect sensor (V2, Microsoft, USA), sampled at 30 Hz, was positioned 1.70 m above and 1.60 m away from the target. Participants performed five free movements per 20-second block, timed to vocal prompts ("go"; "stop"). After a familiarization block with each arm, participants completed three blocks using their non-dominant/paretic hand, followed by three blocks using their dominant/paretic hand. Each block was interspersed with 20 seconds of rest. Then, participants repeated the task for three blocks with each hand under a movement-constrained condition, wherein their shoulders were immobilized to minimize trunk movements.

2.2.2. *Circular steering task*

This task was based on the speed-accuracy trade-off (Besson et al., 2020). Participants were seated on a chair in front of a graphic tablet (A3 size; Wacom, Kazo, Japan) equipped with a stylus affixed to a mouse pad, facing a 24-inch screen projecting a circular target (33-inch circumference) with a 2 cm tunnel. A Kinect was placed above the computer at the height of 1.70 m. The task was delivered using a lab-made software, the LSL-Mouse (<https://github.com/KarimaBak/LSL-Mouse>). Participants were instructed to move a cursor as fast as possible in a clockwise direction. During the familiarization phase, participants were instructed to accelerate if errors (any instances outside the 2 cm circular tunnel boundaries) were below 15% (based on pilot testing). The task comprised three blocks for each arm (20 seconds of task with 20 seconds of rest), commencing with their non-dominant/paretic hand.

2.2.3. *Clinical assessments of paretic upper limb impairment*

In conjunction with the functional kinematics and brain evaluation, patients' UL motor function was appraised through clinical evaluations. We utilized several recognized and validated tests, including the Fugl Meyer Upper-extremity test (FM-UE) (Fugl-Meyer et al., 1975; Gladstone et al., 2002), the Box and Block test (BBT) (Mathiowetz et al., 1985), the Wolf-motor function test (WMFT) (Wolf et al., 2001), the Barthel Index (BI) (Mahoney et Barthel, 1965), and the Proximal-arm non-use (PANU) test (Bakhti et al., 2017, 2018). Comprehensive details of these evaluations are described in the cited references.

The FM-UE assesses upper limb motor capacity, while the BBT measures arm and hand grasping function. WMFT evaluates upper limb function, and the BI measures overall

functional recovery. The PANU test measures the degree to which the paretic upper limb, specifically the shoulder and elbow, is not spontaneously used. These tests collectively provide a comprehensive overview of the paretic upper limb's functional capacity and impairment level in stroke patients.

2.3. Brain activity

Participants wore a custom neoprene head cap equipped with a combined EEG-fNIRS system to monitor brain activity within the left and right sensorimotor cortical regions during both functional motor tasks. We utilized a wireless Starstim fNIRS integration system (Starstim8, Neuroelectronics, Barcelona, Spain; Octamon+, Artinis Medical Systems, Netherlands) to measure EEG and fNIRS signals. Details regarding the placement of the 16 channels, comprising four NIRS and four EEG channels per SM1 hemisphere, are outlined in a previous article (see Figure 1 in Muller et al., 2023).

The EEG electrodes were positioned in and around SM1 cortices: C4, FC2, FC6, CP2 in the right hemisphere and C3, FC1, FC3, CP1 in the left hemisphere, in alignment with the international 10–10 system. The electrodes (NG Geltrode, Neuroelectronics) were filled with electro-gel (Signa Gel®). Using an ear clip, reference electrodes (CMS, DRL) were placed over the right earlobe. The EEG signals were sampled at a rate of 500 Hz. We controlled the wifi-EEG device via a software interface (Neuroelectronics Instrument Controller, NIC v 2.0).

For the fNIRS recording, we used a continuous-wave system employing two wavelengths to capture changes in HbO₂ and HbR overlying the left and right SM1, sampling at 10 Hz. The two receivers were positioned at the C1 and C2 locations of the 10–10 EEG system, with four transmitters placed 3 cm from the receivers using plastic holders. The fNIRS Bluetooth device was managed through a software interface (Oxysoft, v3.2.51.4). Following the equipment setup, participants were asked to perform a wrist extension task to verify if the movement induced a hemodynamic response.

2.4. Data analysis

2.4.1. Task performance

The paced reaching and circular steering task kinematics analysis was done based on previous (Bakhti et al., 2017, 2018, Faity et al., 2022) and LSL-Kinect software (LSL-KinectV2: <https://github.com/KarimaBak/LSL-KinectV2>). For the paced reaching task, we calculated the proximal-arm non-use (%) and the hand mean velocity (mm/s). For both tasks, we calculated as trunk compensation parameter, the range of trunk anterior flexion (°) and the

range of shoulder displacement ($^{\circ}$), representing the use of the trunk (compensation) to realize the reaching movement. And, we calculated, as arm use parameters, the range of elbow extension ($^{\circ}$) and the range of shoulder adduction ($^{\circ}$), representing the use of arm extension to do the movement.

We assessed the speed-accuracy trade-off during the circular steering task using the Index of Performance (IP_e in bits/s) as described by Accot (2001). We calculated the Index of Effective Task Difficulty (ID_e) with the formula: $ID_e = \frac{2\pi R}{W_e}$, where R represents the subject's mean circular path radius, and W_e denotes the effective path width. We determined W_e using MacKenzie's formula (1992): $W_e = \sqrt{2\pi e} * \sigma$, where σ is the standard deviation of the radius. We then computed IP_e by dividing ID_e by the movement time (MT). In addition, we calculated the speed as laps per second and accuracy as bias (W_e/W , following McKenzie et al., 1992) of the movement.

2.4.2. Brain activity (fNIRS and EEG)

We processed all fNIRS raw data using the HOMER toolbox in MATLAB (Homer2 NIRS processing package, Huppert et al., 2009) with the files generated by the Lab Recorder (xdf files). Pre- and post-processing steps are detailed in a previous study (Muller et al., 2023). We used the relative changes in peak HbO2 concentration as an indicator of brain activity.

We analysed all EEG data using the EEGLAB toolbox on MATLAB (Delorme & Makeig, 2004, version 2021.1), with the files generated by the Lab Recorder (xdf files). Details of pre- and post-processing steps are provided in a previous study (Muller et al., 2023). We calculated the event-related spectral perturbations (ERSP) in the alpha (8-13 Hz) and beta (14-29 Hz) rhythms, revealing average power changes in these specific time frequencies. This information provides insight into event-related desynchronization (ERD; power decrease in a specific frequency band relative to baseline, i.e., rest) and synchronization (ERS; power increase in a specific frequency band relative to the task). For EEG and fNIRS analyses, parameters were averaged by tasks (paced reaching; circular steering), hand condition (dominant / non-paretic; non-dominant / paretic), and hemisphere (contralateral / ipsilesional ; ipsilateral / contralesional).

2.5. Statistical analyses

Statistical analyses were performed using R software (version 4.2.1) and the ggplot2 (Wickham, 2016), dplyr (Wickam, 2021) and rstatix (Kassambara, 2021) packages. Parametric

tests were employed following the validation of data normality via the Shapiro-Wilk test and visual examination of Q-Q plots. Effects sizes were indicated using the partial eta square (η^2p), with small (0.02), medium (0.13), and large (0.26) effect sizes noted (Bakeman et al., 2005; Lakens et al., 2013). A threshold of $p < .05$ was used for statistical significance. If necessary, pairwise comparisons were conducted using T-tests, with the Benjamini-Hochberg procedure applied for p-value correction in multiple tests (Benjamini & Hochberg, 1995). Significant effects were interpreted only when of sufficient intensity ($\eta^2p > .02$). All values are presented as mean (SD) unless stated otherwise. In the absence of three-level interaction effects, only two-level interaction effects were reported for each factor combination. Note that the degrees of freedom of the analysis are varied across variables due to differing exclusion rates for subjects.

Tasks performance and kinematics

The movement parameters for the circular steering task (Ipe, speed, accuracy, shoulder displacement, trunk anterior flexion, change of elbow extension, change of shoulder adduction) were evaluated through a mixed ANOVA, which included group (healthy and stroke) as a between-subject factor, and hand (non-paretic/dominant and paretic/non-dominant hand) as a within-subject factor. Similarly, a mixed ANOVA was employed for the paced-reaching task (PANU, mean velocity, shoulder displacement, trunk anterior flexion, change of elbow extension, change of shoulder adduction), incorporating group (healthy and stroke) as a between-subject factor and hand (dominant and non-dominant hand) and condition (spontaneous- SAU and maximal- MAU) as within-subject factors.

Cortical activations

For the analysis of fNIRS peak of ΔHbO_2 and EEG Alpha and Beta ESRPs, a mixed ANOVA was applied with group (healthy and stroke) as a between-subject factor, and hand (non-paretic / dominant and paretic / non-dominant hand), condition (spontaneous- SAU and maximal- MAU, paced-reaching task), and hemisphere (ipsilateral and contralateral to the movement) as within-subject factors.

Brain-movement relationship

In our investigation of the association between performance in the circular steering task and brain activation (fNIRS peak ΔHbO_2) across the groups, we consistently applied Spearman rank correlation analysis. This approach was chosen to account for the non-normal distribution of some variables and to maintain consistency across the analysis, thus enhancing comparability

of our findings. We choose to keep only moderate effects to avoid false effects, thus, we just present correlation with at least a $p < .01$ and a $r_s^2 > .25$. Only those effects were reported to facilitate the results presentation.

3. Results

3.1. Tasks performance and kinematics

Circular steering task (figure 1)

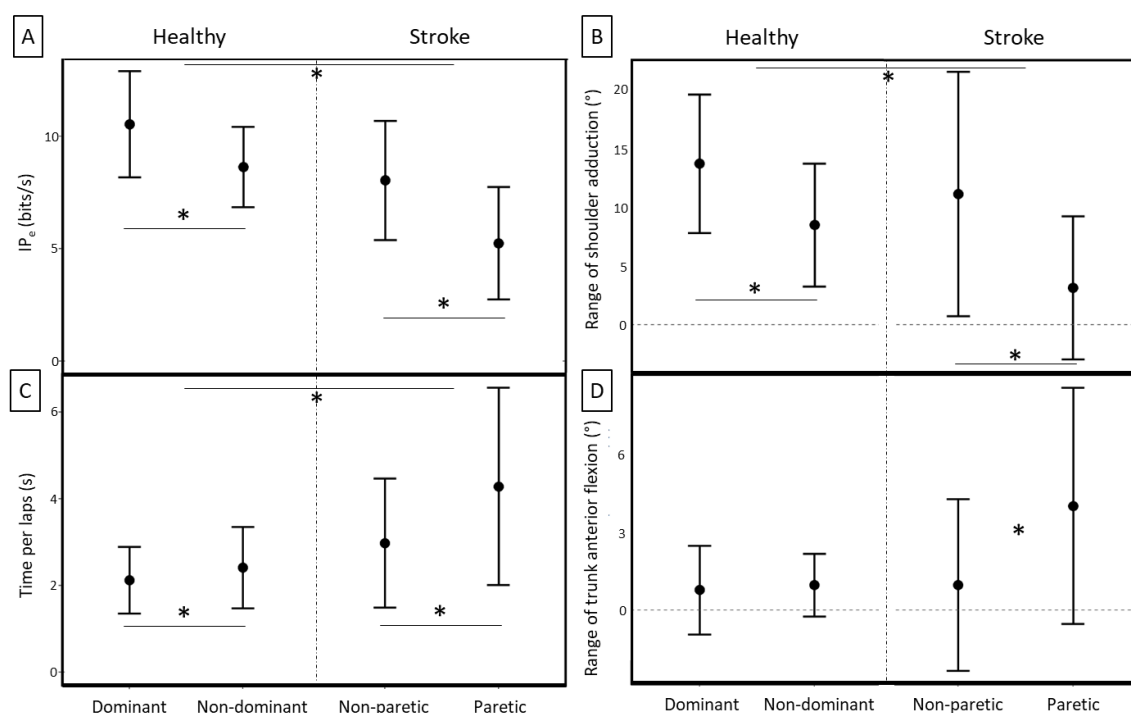


Figure 1. Circular steering task performances and strategies (*mean ± SD*) for the two groups and according to hand trial. A) Index of performance (IP_e); B) Range of shoulder adduction; C) Time per laps; and D) Range of trunk anterior flexion. (* for statistically significant differences at $p < .05$).

We found a higher performance (IP_e) in the healthy group and with the dominant hand / non paretic hand for both groups (Group: $F_{(1,40)} = 20.52$, $p = .000$, $\eta^2_p = .34$; Hand: $F_{(1,40)} = 53.00$, $p = .000$, $\eta^2_p = .57$) with no Group \times Hand interaction ($F_{(1,40)} = 1.97$, $p = .169$, $\eta^2_p = .05$). For the speed component (i.e., time per laps), we found a Group \times Hand interaction ($F_{(1,40)} = 5.83$, $p = .020$, $\eta^2_p = .13$). Post-hoc analysis showed that the time per laps difference between paretic/non-dominant and non-paretic/dominant hand, was significantly higher for the stroke group, with a longer time per laps with the paretic arm (Healthy: $\eta^2_p = .25$; Stroke: $\eta^2_p = .34$). Moreover, it shows that the time per laps was significantly shorter in the healthy group, whatever the hand. For the accuracy component (i.e., bias), we did not find any significant effects.

On the circular steering task, we found that the trunk compensations were higher in the stroke group when performing with the paretic hand (Group x Hand interaction : $F_{(1,35)} = 8.95$, $p = .005$, $\eta^2_p = .20$). For both groups, the range of elbow extension was significantly higher with the dominant / non -paretic hand ($F_{(1,35)} = 8.28$, $p = .007$, $\eta^2_p = .19$). Finally, the range of shoulder adduction was higher in the healthy group, and higher in the dominant / non-paretic hand for both groups (Group : $F_{(1,35)} = 4.63$, $p = .038$, $\eta^2_p = .12$; Hand : $F_{(1,35)} = 17.88$, $p = .000$, $\eta^2_p = .34$).

Paced reaching task (figure 2)

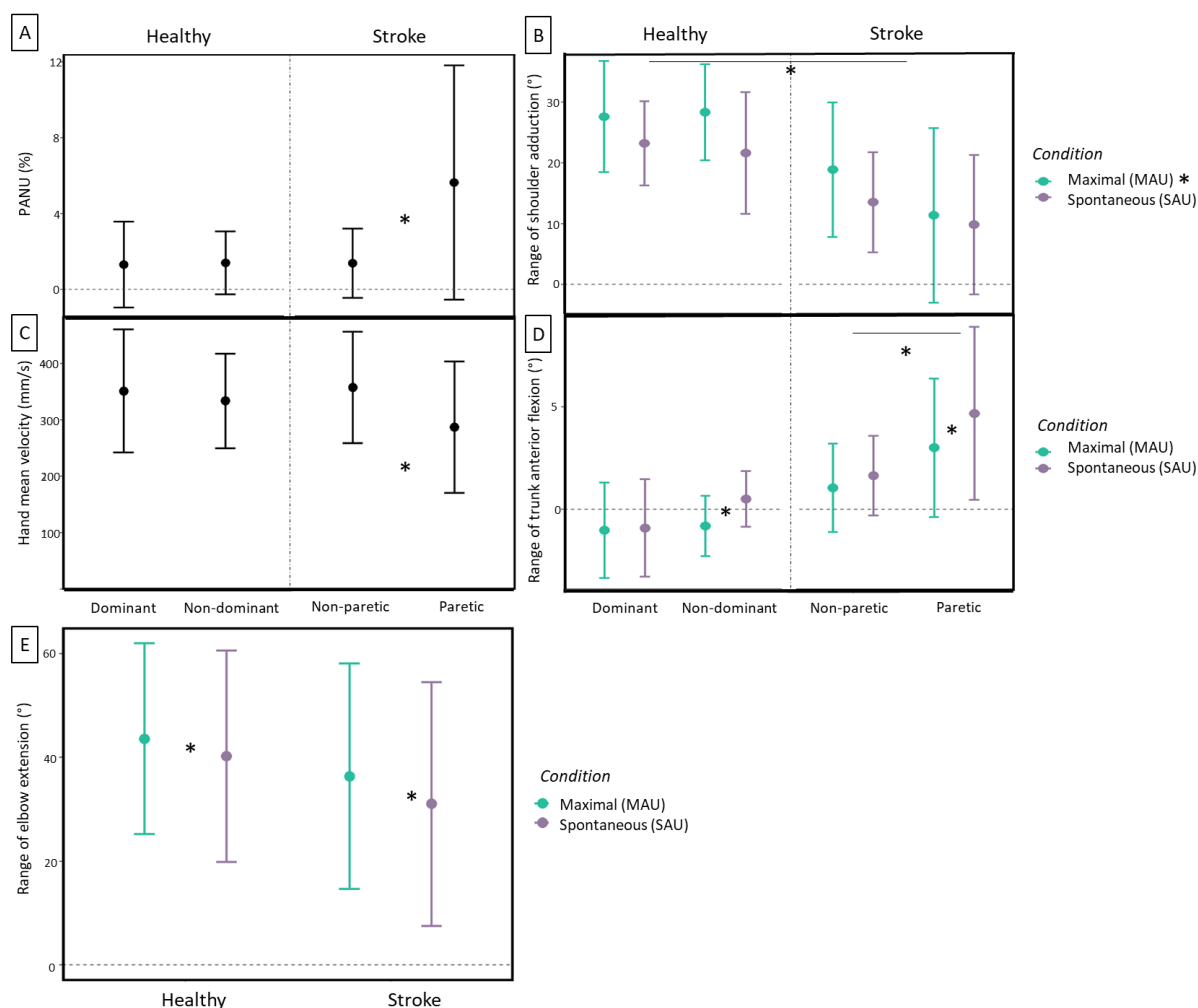


Figure 2. Paced reaching task movement strategies ($mean \pm SD$) for the two groups and according to hand trial and condition (for condition interaction and/or effects). A) Proximal-arm non-use; B) Range of shoulder adduction; C) Hand mean velocity; D) Range of trunk anterior flexion; and E) Range of elbow extension. (* for statistically significant differences at $p < .05$).

On the paced reaching task, we found a Group x Hand interaction on the PANU, range of trunk flexion and hand mean velocity (PANU: $F_{(1,37)} = 8.85$, $p = .005$, $\eta^2_p = .19$; range of trunk

flexion: $F_{(1,37)} = 5.01$, $p = .031$, $\eta^2_p = .12$; hand mean velocity: $F_{(1,37)} = 4.93$, $p = .033$, $\eta^2_p = .12$). The range of trunk anterior flexion, and PANU were higher for the stroke paretic hand and at the same time the hand mean velocity was lower. For the range of trunk anterior flexion, we found a Hand x Condition interaction showing that the range of anterior trunk flexion was lower in the maximal condition for the non-dominant / paretic hand ($F_{(1,37)} = 4.88$, $p = .033$, $\eta^2_p = .12$). We also found a condition effect on the range of elbow extension, for both groups, it was higher in the maximal condition ($F_{(1,37)} = 7.11$, $p = .011$, $\eta^2_p = .16$). Finally, we found that the range of shoulder adduction was higher in the healthy group and in the maximal condition for both groups (Group: $F_{(1,37)} = 25.84$, $p = .000$, $\eta^2_p = .41$; Condition: $F_{(1,37)} = 18.62$, $p = .000$, $\eta^2_p = .34$; Group x Condition: $F_{(1,37)} = 25.84$, $p = .324$, $\eta^2_p = .03$).

2.1. Brain activity

Brain activity (fNIRS: peak of ΔHbO_2 ; EEG: ERD and ERS) during paced reaching and circular steering tasks are presented in figure 3 (fNIRS) and figure 4 (EEG) and the statistical results are detailed in Table 3 (circular steering task) and Table 4 (paced-reaching task) for group, hand, hemisphere, and condition effects and two-level interaction effects with each factor combinations. The significant three-levels interactions are reported in the text.

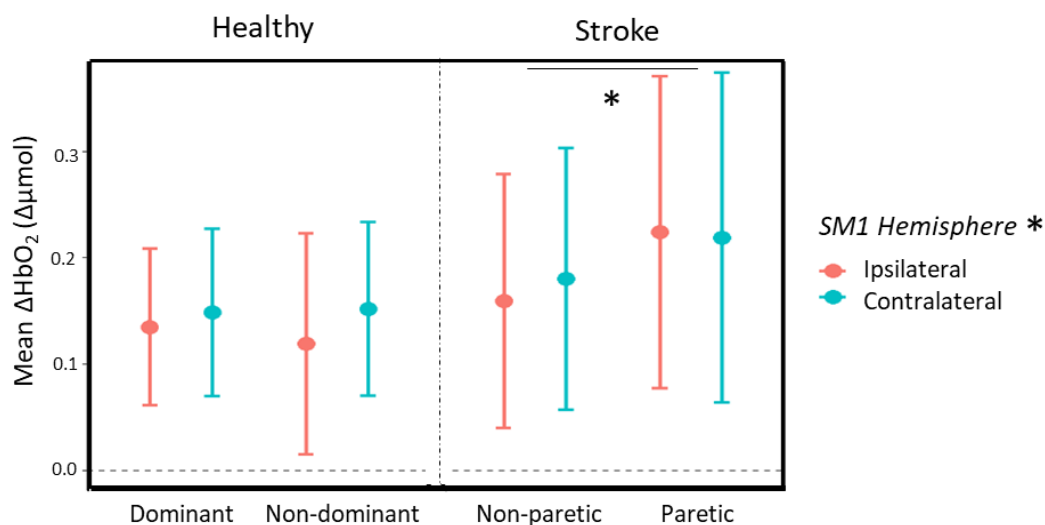


Figure 3. fNIRS main results (*mean* \pm *SD*). Paced reaching task mean ΔHbO_2 peak in function of the group, hand, and hemisphere (ipsilateral in green; and contralateral in violet). * For statistically significant differences at $p < .05$, for hand effect in the stroke group and hemisphere effect for all groups and conditions.

Circular steering task - fNIRS

The analysis of the mean ΔHbO_2 peak during the circular steering task showed no significant effects.

Paced reaching task – fNIRS (figure 3)

The analysis of the mean ΔHbO_2 peak during the paced reaching task showed a higher activation for stroke group with the paretic hand (Group x Hand: $F_{(1,36)} = 4.51$, $p = .041$, $\eta^2_p = .11$) and a higher activation in the contralateral side compared to the ipsilateral one for both groups (Hemisphere: $F_{(1,36)} = 6.45$, $p = .016$, $\eta^2_p = .15$).

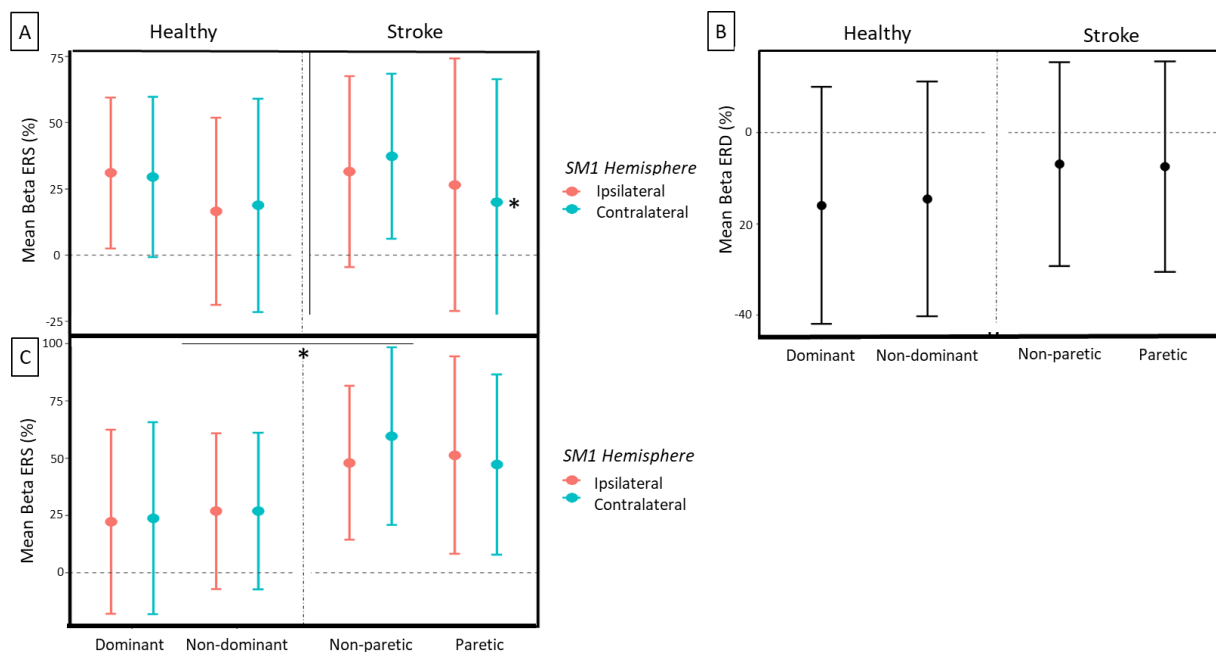


Figure 4. EEG main results ($mean \pm SD$). A) Circular steering task mean Beta ERS with a lower post-movement synchronization in contralateral hemisphere (violet line) during paretic movement. B) Paced reaching task mean Beta ERD with a tendency to lower ERD in the stroke group. C) Paced-reaching task mean Beta ERS with a higher post-movement synchronization in the stroke group for both hemispheres. (* for statistically significant differences at $p < .05$)

Circular steering task – EEG

On the circular steering task, we found on Beta ERS a double interaction Group x Hand x Hemisphere ($F_{(1,25)} = 5.02$, $p = .034$, $\eta^2_p = .17$). Post-hoc comparisons revealed that, on the stroke group, there was a Hand x Hemisphere interaction ($F_{(1,14)} = 7.56$, $p = .016$, $\eta^2_p = .35$) showing a lower post-movement synchronization in the contralateral / ipsilesional hemisphere when performing with the paretic hand (see figure 4). The analysis of the mean ERSP did not show any main effect of Group on Alpha and Beta ERD nor Alpha ERS.

Reaching task – EEG (figure 4)

On the paced reaching task showed a Group x Brain interaction on the Beta ERD ($F_{(1,23)} = 4.98$, $p = .036$, $\eta^2_p = .19$). We found a tendency to a Group effect ($F_{(1,129)} = 3.88$, $p = .051$, $\eta^2_p = .03$) showing a lower movement desynchronization in the stroke group, but the comparison between the different modalities of the Group x Brain interaction were too low to emerge (see

figure 4). On the Alpha ERD we did not find any significant effect. On the Beta ERS, we found a Hand x Condition interaction showing that for the stroke group, the post-movement synchronization was higher on the maximal condition ($F_{(1,21)} = 8.80$, $p = .007$, $\eta^2_p = .30$). We also found a double interaction between Group x Hand x Hemisphere ($F_{(1,21)} = 5.08$, $p = .035$, $\eta^2_p = .20$). Post-hoc comparison revealed a Hand x Brain interaction for the stroke group ($F_{(1,27)} = 14.9$, $p = .001$, $\eta^2_p = .36$) showing a Brain effect on the Beta ERS with the dominant / non-paretic hand in the stroke group. On the Alpha ERS, we found a Group x Hemisphere interaction ($F_{(1,16)} = 4.53$, $p = .049$, $\eta^2_p = .22$). Post-hoc comparisons revealed that there was a Group effect in the ipsilateral hemisphere ($F_{(1,53)} = 28.8$, $p = .000$, $\eta^2_p = .35$), showing a higher post-movement synchronization in the ipsilateral hemisphere of the stroke group in comparison to the healthy group. Finally, we found a Hand x Hemisphere interaction ($F_{(1,16)} = 6.28$, $p = .023$, $\eta^2_p = .28$). Post-hoc comparison revealed a hand effect in the contralateral hemisphere ($F_{(1,51)} = 4.70$, $p = .035$, $\eta^2_p = .08$), with a higher post-movement synchronization in the non-dominant / paretic hand.

Table 3. Statistical results of the ANOVA on the EEG and fNIRS brain parameters for the circular steering task.

	GROUP	HEMISPHERE	HAND
A.			
<i>EEG</i>			
Alpha ERD	F (1, 27) = 0.66, p = .424, $\eta^2_p = .02$	F (1, 27) = 1.45, p = .293, $\eta^2_p = .04$	F (1, 27) = 0.42, p = .523, $\eta^2_p = .01$
Beta ERD	F (1, 27) = 0.08, p = .780, $\eta^2_p = .00$	F (1, 27) = 0.21, p = .654, $\eta^2_p = .01$	F (1, 27) = 0.40, p = .534, $\eta^2_p = .01$
Alpha ERS	F (1, 25) = 1.28, p = .269, $\eta^2_p = .05$	F (1, 25) = 0.00, p = .956, $\eta^2_p = .00$	F (1, 25) = 2.76, p = .109, $\eta^2_p = .09$
Beta ERS	F (1, 25) = 0.15, p = .698, $\eta^2_p = .01$	F (1, 25) = 0.00, p = .996, $\eta^2_p = .00$	F (1, 25) = 2.45, p = .127, $\eta^2_p = .09$
<i>fNIRS</i>			
Δ HbO ₂ peak	F (1, 31) = 0.00, p = .967, $\eta^2_p = .00$	F (1, 31) = 0.20, p = .659, $\eta^2_p = .00$	F (1, 31) = 0.45, p = .506, $\eta^2_p = .01$
B.	GROUP x HEMISPHERE	GROUP x HAND	HAND x HEMISPHERE
<i>EEG</i>			
Alpha ERD	F (1, 27) = 0.00, p = .999, $\eta^2_p = .00$	F (1, 27) = 1.04, p = .317, $\eta^2_p = .04$	F (1, 27) = 1.78, p = .193, $\eta^2_p = .06$
Beta ERD	F (1, 27) = 0.56, p = .461, $\eta^2_p = .02$	F (1, 27) = 0.90, p = .351, $\eta^2_p = .03$	F (1, 27) = 0.25, p = .619, $\eta^2_p = .01$
Alpha ERS	F (1, 25) = 0.26, p = .614, $\eta^2_p = .01$	F (1, 25) = 0.00, p = .961, $\eta^2_p = .00$	F (1, 25) = 0.07, p = .792, $\eta^2_p = .00$
Beta ERS	F (1, 25) = 0.03, p = .868, $\eta^2_p = .00$	F (1, 25) = 0.00, p = .924, $\eta^2_p = .00$	F (1, 25) = 1.42, p = .244, $\eta^2_p = .05$
<i>fNIRS</i>			
Δ HbO ₂ peak	F (1, 31) = 0.07, p = .791, $\eta^2_p = .02$	F (1, 31) = 1.40, p = .246, $\eta^2_p = .04$	F (1, 31) = 3.52, p = .070, $\eta^2_p = .10$

A. Effects of Group (Old healthy vs Stroke), Hemisphere (Contralateral vs Ipsilateral) and Hand (Dominant / Non-paretic vs Non-dominant / Paretic) on the fNIRS and EEG parameters on the circular steering task and **B.** Two levels interactions of the model. In bold, results with $p < .05$ and $\eta^2_p > .0$

Table 4. Statistical results of the ANOVA on the EEG and fNIRS brain parameters for the paced-reaching task.

	GROUP	HEMISPHERE	HAND	CONDITION
<i>EEG</i>	Alpha ERD	F (1, 23) = 0.00, p = .997, $\eta_p^2 = .00$	F (1, 23) = 0.08, p = .770, $\eta_p^2 = .00$	F (1, 23) = 0.49, p = .492, $\eta_p^2 = .02$
	Beta ERD	F (1, 23) = 2.81, p = .107, $\eta_p^2 = .11$	F (1, 23) = 0.02, p = .896, $\eta_p^2 = .00$	F (1, 23) = 0.12, p = .734, $\eta_p^2 = .01$
	Alpha ERS	F (1, 16) = 8.62, p = .010, $\eta_p^2 = .35$	F (1, 16) = 52.21, p = .000, $\eta_p^2 = .77$	F (1, 16) = 0.01, p = .927, $\eta_p^2 = .00$
	Beta ERS	F (1, 21) = 5.44, p = .030, $\eta_p^2 = .21$	F (1, 21) = 2.46, p = .132, $\eta_p^2 = .11$	F (1, 21) = 1.24, p = .278, $\eta_p^2 = .06$
<i>fNIRS</i>	ΔHbO_2 peak	F (1, 36) = 5.93, p = .020, $\eta_p^2 = .14$	F (1, 36) = 1.45, p = .016, $\eta_p^2 = .15$	F (1, 36) = 1.49, p = .231, $\eta_p^2 = .04$
		GROUP x HEMISPHERE	GROUP x HAND	HAND x CONDITION
<i>EEG</i>	Alpha ERD	F (1, 23) = 0.50, p = .828, $\eta_p^2 = .02$	F (1, 23) = 0.08, p = .776, $\eta_p^2 = .00$	F (1, 23) = 0.23, p = .634, $\eta_p^2 = .01$
	Beta ERD	F (1, 23) = 4.98, p = .036, $\eta_p^2 = .18$	F (1, 23) = 0.05, p = .831, $\eta_p^2 = .00$	F (1, 23) = 0.08, p = .786, $\eta_p^2 = .00$
	Alpha ERS	F (1, 16) = 4.53, p = .049, $\eta_p^2 = .22$	F (1, 16) = 0.39, p = .539, $\eta_p^2 = .02$	F (1, 16) = 0.15, p = .704, $\eta_p^2 = .00$
	Beta ERS	F (1, 21) = 1.83, p = .191, $\eta_p^2 = .08$	F (1, 21) = 1.36, p = .257, $\eta_p^2 = .06$	F (1, 21) = 8.80, p = .007, $\eta_p^2 = .29$
<i>fNIRS</i>	ΔHbO_2 peak	F (1, 36) = 1.98, p = .168, $\eta_p^2 = .05$	F (1, 36) = 4.51, p = .041, $\eta_p^2 = .11$	F (1, 36) = 2.72, p = .108, $\eta_p^2 = .07$
		HAND x HEMISPHERE	HEMISPHERE x HAND	HEMISPHERE x CONDITION
<i>EEG</i>	Alpha ERD	F (1, 23) = 1.57, p = .223, $\eta_p^2 = .06$	F (1, 23) = 0.59, p = .451, $\eta_p^2 = .02$	
	Beta ERD	F (1, 23) = 1.04, p = .320, $\eta_p^2 = .00$	F (1, 23) = 0.07, p = .796, $\eta_p^2 = .00$	
	Alpha ERS	F (1, 16) = 6.28, p = .023, $\eta_p^2 = .28$	F (1, 16) = 0.11, p = .746, $\eta_p^2 = .01$	
	Beta ERS	F (1, 21) = 6.80, p = .020, $\eta_p^2 = .23$	F (1, 21) = 0.05, p = .831, $\eta_p^2 = .00$	
<i>fNIRS</i>	ΔHbO_2 peak	F (1, 36) = 0.05, p = .823, $\eta_p^2 = .00$	F (1, 36) = 0.77, p = .387, $\eta_p^2 = .02$	

A. Effects of Group (Old healthy vs Stroke), Hemisphere (Contralateral vs Ipsilateral) and Hand (Dominant / Non-dominant / Paretic) on the fNIRS and EEG parameters on the paced-reaching task and **B.** Two levels interactions of the model. In bold, results with $p < .05$ and $\eta_p^2 > .0$

2.2. Brain-movement-clinical scores relationship

Brain-movement

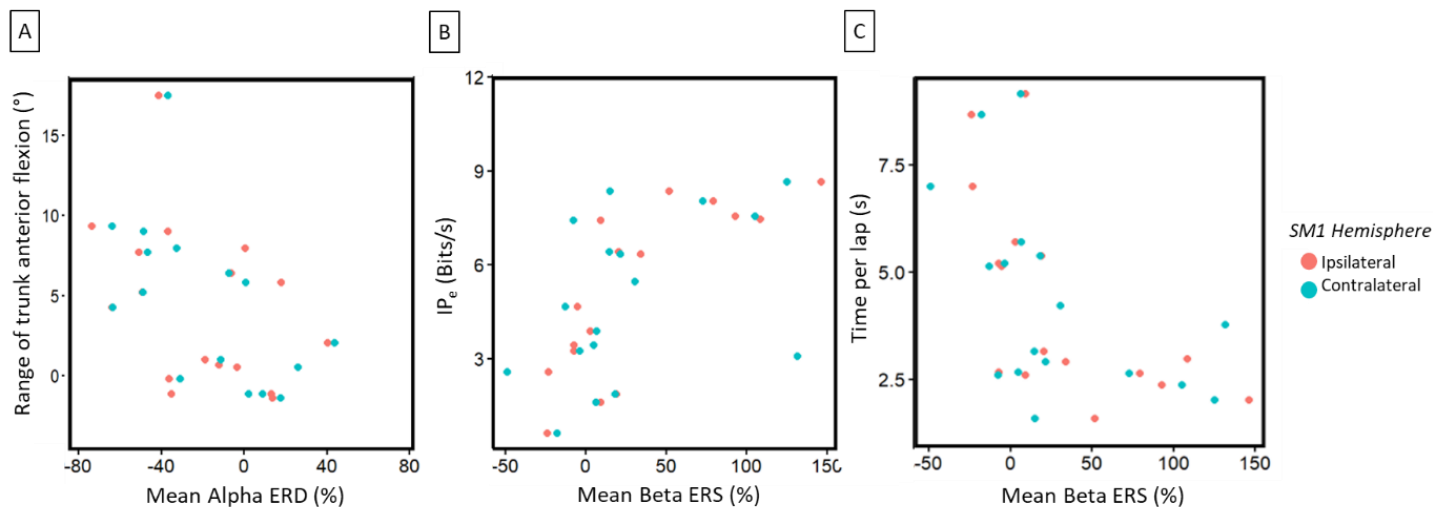


Figure 5. Correlation between A) Alpha ERD and the trunk use, and B) Beta ERS and the index of effective performance (IP_e), during the circular steering task with the paretic hand.

The spearman rank analysis highlighted, for the stroke group, in the circular steering task with paretic hand, an increased use of the trunk was associated to higher movement desynchronization on the contralateral hemisphere and a tendency in the ipsilateral one (Contralateral : $p = .007$, $r_s^2 = .44$; Ipsilateral : $p = .080$, $r_s^2 = .19$, see figure 5).

We also found that for the stroke group, for a higher IP_e and time per lap in the circular steering task, there were a higher post-movement synchronization in the ipsilateral hemisphere and a tendency in the contralateral one (IP_e - Ipsilateral : $p = .000$, $r_s^2 = .69$; Contralateral : $p = .050$, $r_s^2 = .24$; Time per lap – Ipsilateral : $p = .000$, $r_s^2 = .49$; Contralateral : $p = .031$, $r_s^2 = .28$, see figure 5).

When reaching in the maximal condition, we found that elbow extension in the stroke group was negatively correlated to the ipsilateral peak of ΔHbO_2 ($p = .008$; $r_s^2 = .32$, see figure 6). We also found that the slower to do the maximal reaching have a higher post-movement synchronization in the ipsilateral hemisphere ($p = .003$, $r_s^2 = .47$, see figure 6).

We found that for a higher spontaneous elbow extension on the reaching task, the Beta post-movement synchronisation was higher (Ipsilateral : $p = .001$, $R^2 = .50$; Contralateral : $p = .000$, $r_s^2 = .62$). On the same conditions, the Alpha post-movement synchronization on the ipsilateral hemisphere was also positively correlated to elbow extension ($p = .009$, $r_s^2 = .37$, see figure 6).

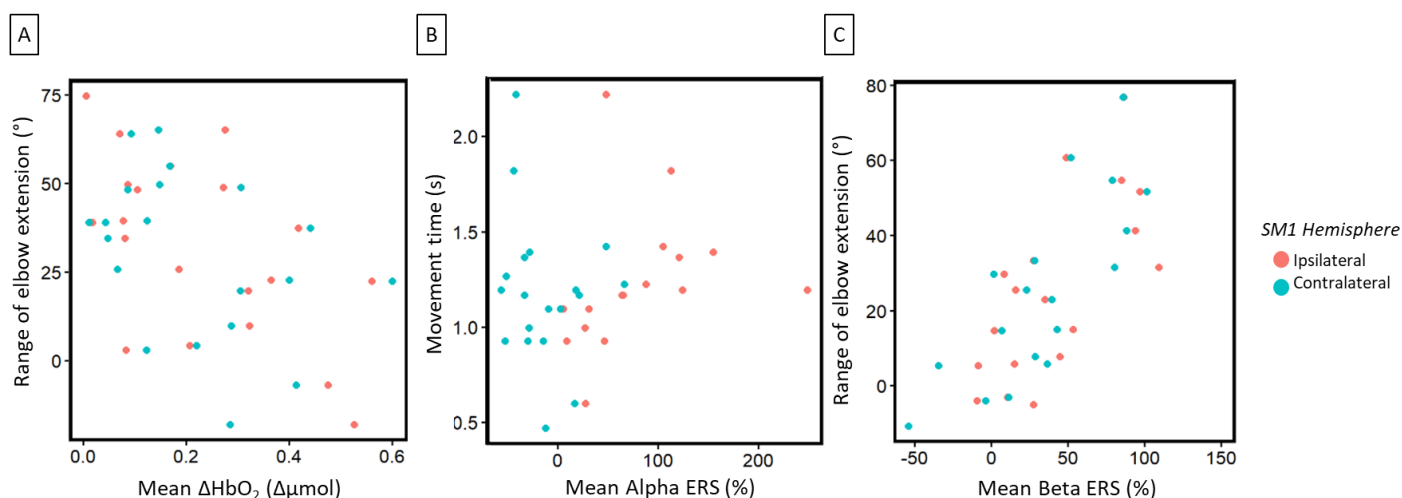


Figure 6. Correlation during the paretic movement of the paced-reaching task between A) Peak of ΔHbO_2 and elbow extension, B) Alpha ERS and movement time, and C) Mean Beta ERS and elbow extension.

Brain-clinical scores

On the correlation between the brain parameters and the clinical scores, we found that a more marked Alpha ERD on the circular steering task was associated to a lower FM-UE (Paretic hand - Ipsilateral : $p = .000$, $r_s^2 = .62$; Paretic hand – Contralateral : $p = .000$, $r_s^2 = .55$; Non-paretic hand - Ipsilateral : $p = .003$, $r_s^2 = .43$; Non-paretic hand – Contralateral : $p = .006$, $r_s^2 = .40$, see figure 7).

On the maximal condition of the reaching task with the paretic hand, we found a negative correlation between the peak of ΔHbO_2 and FM-UE, showing that for a better clinical score there was a lower ipsilateral peak of ΔHbO_2 with a tendency for the contralateral one (Ipsilateral : $p = .003$, $r_s^2 = .37$; Contralateral : $p = .033$, $r_s^2 = .23$, see figure 7).

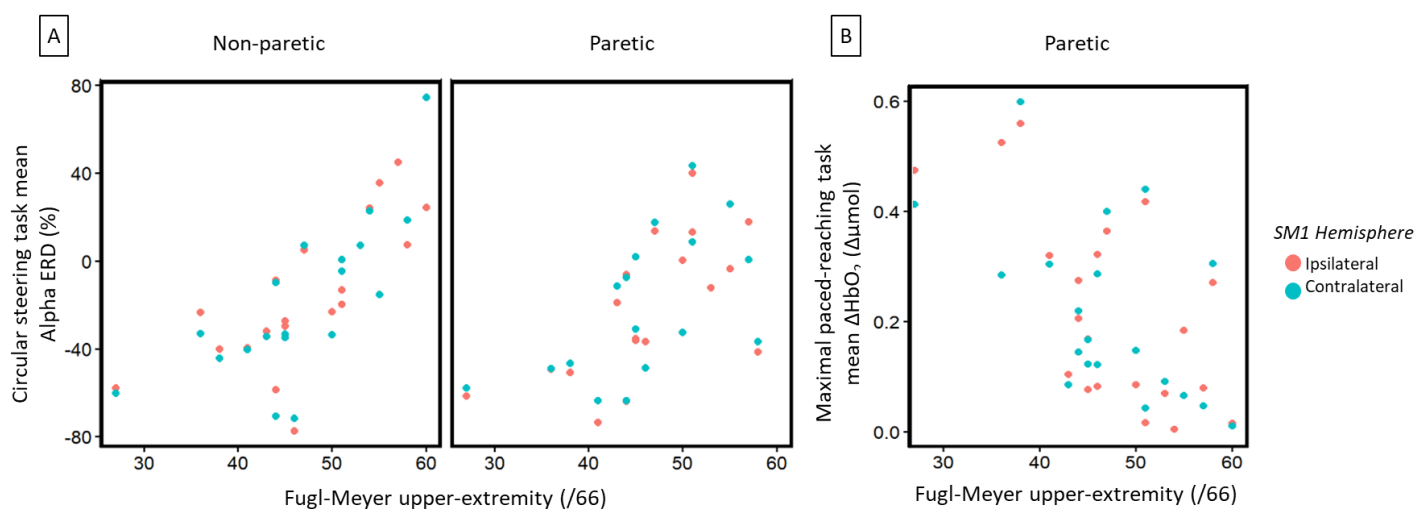


Figure 7. Correlation between A) Alpha ERD during the circular steering task and the FM-UE test and, B) Peak of ΔHbO_2 during the maximal paced-reaching task with the paretic arm and the FM-UE test.

Clinical scores and kinematics (see figure 8)

Looking to the correlations between clinical scores and kinematics of the movement, we found that a higher elbow extension and a higher hand mean velocity during the reaching task with paretic UL was associated to a higher score at the WMFT (Elbow extension - Maximal condition : $p = .006$, $r_s^2 = .37$; Spontaneous condition : $p = .004$; $r_s^2 = .38$; Hand mean velocity – Maximal : $p = .000$, $r_s^2 = .59$, Spontaneous : $p = .002$, $r_s^2 = .45$). The paretic hand mean velocity was also positively correlated to the FM-UE (Maximal : $p = .000$, $r_s^2 = .72$; Spontaneous : $p = .008$; $r_s^2 = .32$).

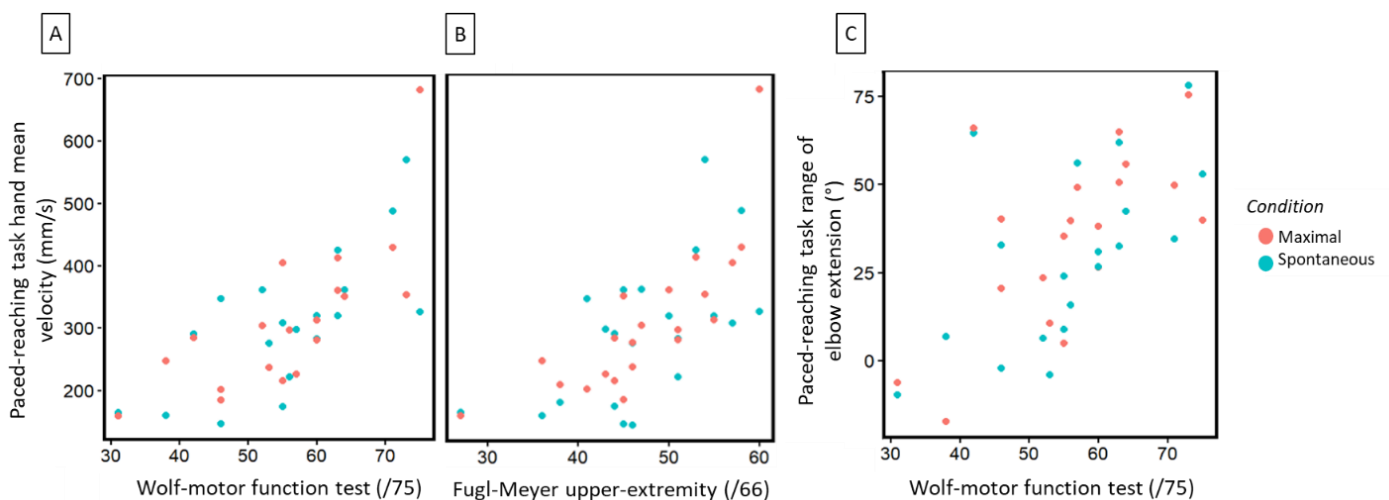


Figure 8. Correlation between paced reaching task hand mean velocity with paretic hand and A) WMFT and B) FM-UE, and C) elbow extension with the paretic arm and the WMFT.

3. Discussion

This study is the first to investigate the brain activity and kinematics changes related to functional movement during unilateral proximal UL motor performance following a stroke. For that purpose, we concurrently recorded SM1 cortical activity via combined fNIRS/EEG, along with UL movements using kinematic tracking. Two previously established functional tasks were employed: a paced-reaching task and a circular steering task designed to interrogate the speed-accuracy trade-off (Bakhti et al., 2017; Muller et al., 2023). The main objective of this study was to evaluate the impact of chronic stroke on the bilateral SM1 electrical (EEG) and hemodynamic (fNIRS) responses during unilateral proximal UL movements. Our key findings include increased brain activity (peak ΔHbO_2) for the paretic hand during the paced-reaching task. Furthermore, during the circular steering task, EEG and kinematic analyses disclosed that enhanced trunk flexion was linked to greater desynchronization in EEG Beta band power, and a higher performance (IP_e) was associated to higher post-movement Beta synchronization. We

also found that greater use of elbow extension was associated to a lower fNIRS SM1 activity and, to higher post-movement EEG Beta synchronization. On movement modifications, we observed that stroke patients exhibited slower speeds, increased compensation, and decreased active use of the elbow-shoulder joint, particularly on the paretic side.

The main finding of this study was the greater increase in SM1 activation detected with fNIRS during the paced reaching movement with the paretic hand which tend to coincide with reduced EEG Beta desynchronization at the onset of movement. These results might indicate compensatory brain mechanisms designed to mitigate the effects of stroke on movement execution. The EEG findings presented a lower SM1 excitability in the stroke group, which was associated to an increased activation of the SM1 (fNIRS) when moving the paretic hand. This aligns with previous studies suggesting reduced brain asymmetry and increased activity as potential mechanisms of post-stroke motor recovery (Tecchio et al., 2007; Levin et al., 2009). These findings can also be compared to the study by Lim and Eng (2019) which analysed fNIRS activity during a modified Box & Block forward reaching test in stroke patients compared to a healthy cohort. Despite the inferior performance, stroke patients demonstrated increased lesioned hemisphere activity during paretic reaching.

For the circular steering task, our findings indicated a reduced performance in the stroke group, while task-related fNIRS peak and EEG-ERD remained comparable across both groups. This task relies heavily on visuomotor control: continuous monitoring and rectification of the trajectory while moving as fast as possible, embodying the concept of the continuous speed-accuracy trade-off (Fitts, 1954). Given these extensive requirements on sensorimotor control networks, this task is a good measure of neural efficiency, i.e., the amount of neural resources required to execute a given task (Kelly & Garavan, 2005). In this context, the hypothesis of neural efficiency postulates that individuals with higher cognitive ability exhibit lower energy consumption in the brain for equivalent tasks (Haier et al., 1992). Given the decreased performance in the stroke cohort and similar brain activity levels, it could be inferred that these individuals exhibit reduced neural efficiency when performing the circular steering task. However, as our study was confined to the SM1 region, we cannot draw a definitive conclusion regarding overall neural efficiency. Indeed, the circular steering task demands a significant level of visuomotor control, and previous research has suggested that the frontal area plays a substantial role in controlling such movements (Sakurada et al., 2018). However, despite the potential impairment of neural efficiency in SM1, the absence of significant brain modification in stroke patients may be explained by considering the task's nature. Indeed, the task required

maximal performance from the healthy subjects as well. Moreover, our previous study found no effects of healthy aging on the level of activity (peak of ΔHbO_2) in this task, as older adults engaging both hemispheres to compensate for their reduced neural efficiency (Muller et al., 2023). We can thus hypothesize that when performance is maximized ("as fast and precise as possible") for all participants, brain activity will reach its maximum, and compensatory mechanisms may rely on alternative neural pathways, such as the frontal areas (Sakurada et al., 2018). Our previous work also indicated no significant effects of healthy aging on any brain or kinematics parameters during the reaching task. This lack of effect underscores the notion that the reaching task was, for our healthy adults, considerably simpler and less demanding than the circular steering task. However, in the present study, we observed modifications in brain activity during the reaching task, potentially due to its complexity for post-stroke patients already demonstrating motor compensation to complete the task successfully.

Focusing on the stroke-induced alterations in movement, we observed the deployment of compensatory strategies by stroke patients to accomplish both functional tasks using their paretic UL. Specifically, in the circular steering task, stroke patients employed their trunk to facilitate task completion with their paretic hand, concomitantly showing reduced use of the elbow-shoulder joints. Similarly, during the reaching task, we detected evidence of proximal-arm non-use (i.e., non-mandatory trunk compensation) when the task was performed with the paretic hand. Additionally, the velocity of the paretic hand was reduced, a finding of particular interest given our use of paced reaching, indicating that the stroke patients were moving slowly to follow the paced rhythm. This result could be explained by the existence of strong correlations between clinical scores and velocity implying that the patients' movement difficulties may be attributed to their level of impairment. This observation is consistent with prior studies demonstrating that the speed of the paretic movement is slower than that of the non-paretic movement (Kamper et al., 2002). This also aligns with our findings from the circular steering task, indicating reduced movement speed in the stroke group, particularly for the paretic arm.

Exploring the connection between brain modifications and kinematic compensations, we identified an association between trunk use and Alpha desynchronization in the circular steering task. This could imply that trunk use necessitates mobilizing increased neuronal resources across both hemispheres. Further, we detected alterations in post-movement Beta synchronization associated with motor performance. Specifically, a higher IP_e correlated with increased ERS. We could hypothesize that, in this task, the high demand level is sustained by

the highest-performing subjects, who are also likely to move fastest. It is well established that increased speed correlates with higher neural activity (Tazoe et al., 2013), implying that the ratio between the movement and rest period could be higher. Regarding the reaching task, we observed different effects depending on whether the task was performed spontaneously or maximally. In the spontaneous reaching task, our findings mirror those of the circular task, with higher post-movement synchronization observed in better performers. Conversely, the positive correlation between movement time and Alpha ERS in the maximal condition is more challenging to explain. One could hypothesize that the enhanced synchronization for slower performers might be explained by the extended duration of neural demand they experience during the task. As they move slower, their SM1 will be engaged for a longer time (i.e., the paced reaching task typically entails 2 seconds of movement and 2 seconds of rest), leading to higher synchronization in the Event-Related Spectral Perturbation (ERSP). Nevertheless, the negative correlation between brain activity (peak of ΔHbO_2) and elbow extension could be akin to the circular steering task, could suggest an over-activation in lower performers who engage their trunk to facilitate movement.

Another hypothesis could be that in the maximal condition, we instruct patients to use their elbow-shoulder joints maximally. Consequently, those who employ these joints less frequently will likely require more resources and increased brain activity. Thus, we could observe either the effect of trunk use or the effect of effort. However, our measurements cannot discern which hypothesis is closer to the truth (i.e., a measure of perceived effort could have been beneficial).

Lastly, an exploratory aim of this study was to investigate the association between stroke patients' clinical scores and the corresponding kinematics and brain parameters.

Clinical scores vs Kinematics:

In terms of clinical scores and kinematic relationships, we found that a higher movement speed and more elbow extension during the paced reaching task correlated positively with higher clinical score. While correlations between kinematic parameters and clinical scores are anticipated (Van Dokkum et al., 2014), the strength of these correlation is not exceedingly high, potentially attributable to the ceiling effect observed with clinical scores (Schwarz et al., 2019). Regardless, our study reinforces the synergistic utility of kinematic and clinical assessments. For instance, high-speed movement training could augment the intensity of task-specific training (Dejong et al., 2012). More specifically, focusing on specific upper limb movements, such training could engender improvements in functional reaching (Hammerbeck et al.,

2017). Therefore, concentrating on the speed component of the paretic arm in specific upper limb movement could be beneficial for functional upper limb recovery. Through the evaluation methods presented in this study, we can offer additional and precise insights regarding the speed component of a functional upper limb movement, thereby facilitating its monitoring throughout rehabilitation.

Brain vs Clinical scores:

Finally, considering the relationship between brain parameters and clinical scores, we observed meaningful correlations that underscore the potential of fNIRS and EEG methodologies in the context of stroke rehabilitation (Teo et al., 2016; Huo et al., 2021; Lim & Eng., 2019). First, we found that a more pronounced Beta desynchronization at movement was linked to a lower score on the FM-UE. It is in line with prior research illustrating that a more significant event-related desynchronization in the sensorimotor cortex correlates with an enhanced demand for concentration and excitatory drive of pyramidal cells during task execution (Monge-Pereira et al., 2014). For example, studies on grip tasks during rehabilitation have shown that with progression and motor improvement, there is a reduced requirement for cortical engagement and effort to perform the grip task (Gonzales-Rosa et al., 2015). Secondly, the inverse correlation between brain activity (peak of ΔHbO_2) and FM-UE indicates that a lower clinical score corresponds with an increased activation during the execution of the paced-reaching task. This is plausible considering the kinematics of the task. We found an association between increased elbow extension and improved WMFT scores. This suggests that patients who utilize their arm extension more during the reaching task will have higher FM-UE scores. It is also known that elbow extension negatively correlates with trunk compensation (Bakhti et al., 2017; Faity et al., 2022). Consequently, patients with greater upper limb deficits may rely more on their trunk to reach the target, leading to larger brain activity in response to the increased demand for the trunk.

This study has several limitations. Due to technical issues with the EEG device, fewer healthy older subjects were included in the analysis. Furthermore, age and gender matching were not strictly adhered to, with a more balanced male/female ratio in the healthy group, which was also older than the stroke group (mean age for healthy group = 72 yrs., stroke group = 64 yrs.; male/female ratio for healthy group = 11 women; stroke group = 8 women). Additionally, the two groups were not tested in the same experimental location; healthy subjects underwent the experiment in a laboratory setting, whereas stroke subjects were assessed at a hospital. Nonetheless, bias was minimized as both groups were evaluated in quiet, isolated rooms, and

the experimental setup and evaluator remained consistent. Lastly, the reaching task, paced at a consistent rhythm for all participants, could present a significant limitation. This speed constraint could lead to an augmented use of compensatory movements in stroke patients to reach the ball at the required speed (Mandon, 2016).

4. Conclusion

In conclusion, this study provides insight into the impacts of stroke on the task-related brain activity and kinematics during unilateral upper limb movements that engage full UL joint movements (i.e., shoulder, elbow, wrist). Our findings highlight the brain and movement compensations associated with a chronic post-stroke population. Additionally, we demonstrate the utility of a combined fNIRS-EEG recording approach, which correlates with kinematic and clinical scores. The concurrent evaluation of brain and kinematic parameters offers complementary information about the execution of paretic movements, allowing for extracting specific components for targeted intervention during rehabilitation. Moreover, these measures can enrich routine clinical assessments in ecological settings. As perspectives, the ReArm project, of which this study is a part, aims to discern the effects of rehabilitation on these specific brain and kinematic parameters. Furthermore, we aim to investigate their applicability in routine evaluation to facilitate more personalized rehabilitation strategies. Through these efforts, we hope to contribute meaningfully to the evolving landscape of stroke rehabilitation research.

Declaration of Competing Interest

The authors have no conflict of interest to declare.

Funding

This research is part of the ReArm project. It is funded by the Direction générale de l'offre de soins (DGOS) in the French Ministère des Affaires Sociales et de la Santé (Programme hospitalier de recherche infirmière et paramédicale-PHRIP-2018-0731).

Data availability

Data and scripts, will be made available on request.

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8.3. Chapter and personal contribution part key-points

STROKE EFFECTS ON TASK-RELATED BRAIN ACTIVITY AND KINEMATICS

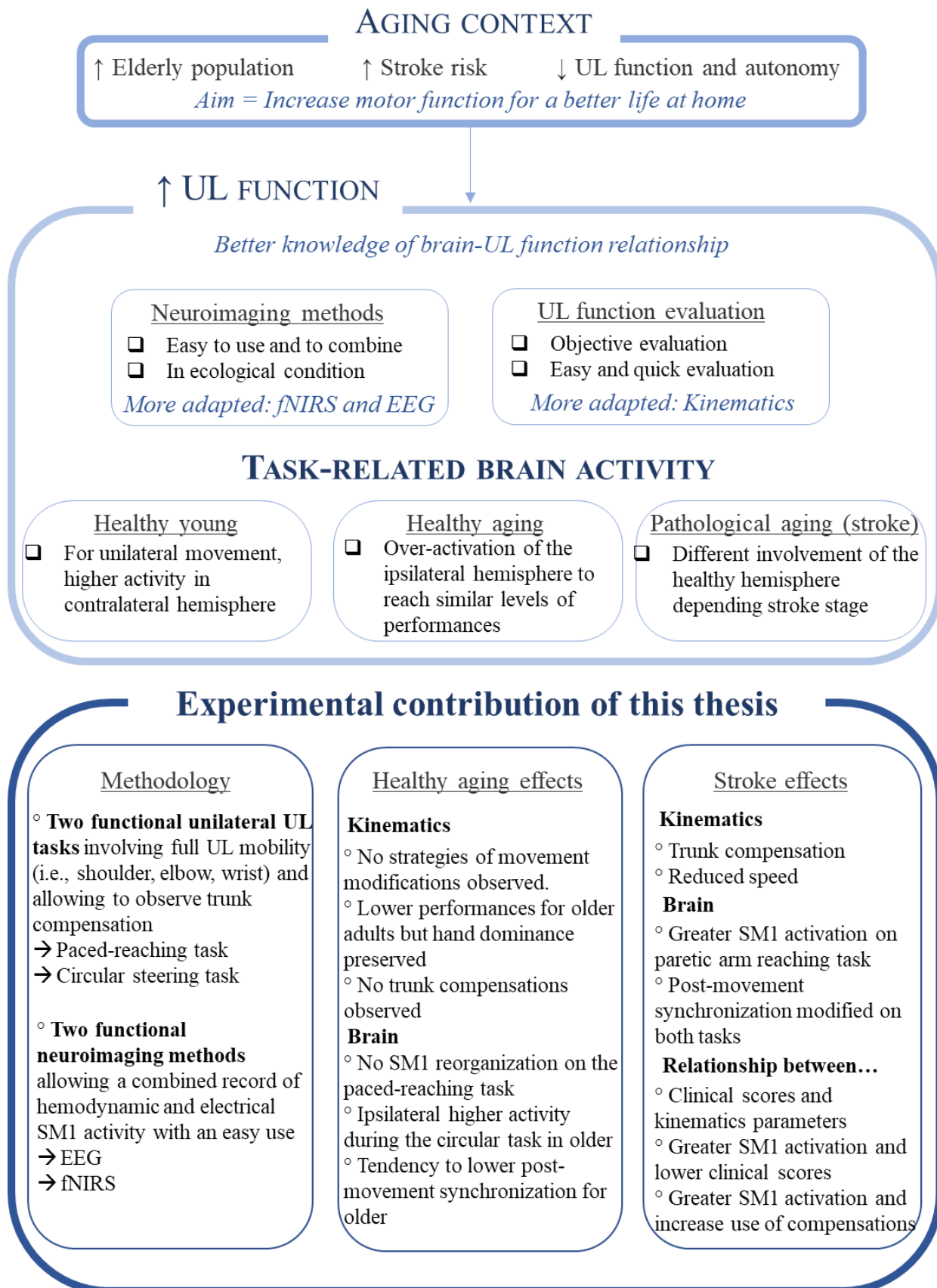
- **Aim** – Unveil the stroke effects in the brain hemodynamic and electrical oscillation patterns during unilateral multi-joint UL movements.
- **Methods** – Combined fNIRS-EEG system was synchronized with movement capture system to record SM1 activation on 21 old controls (mean age = 73 yrs.) and 21 chronic post-stroke patients (mean age = 64 yrs.)
- **Results** –
 - Movement strategies:
 - Stroke patients were slower and especially with paretic arm
 - Stroke patients were using more compensations and thus less active use of elbow-shoulder joint especially with paretic arm
 - Brain modifications:
 - Post-movement synchronization (EEG) modified in both tasks
 - Greater activation (fNIRS peak) and lower desynchronization (Beta EEG) on the reaching task with paretic arm
 - Brain-kinematics-clinical scores relationships
 - Greater SM1 activation during reaching task associated to lower clinical score
 - Movement compensation associated to higher SM1 activation
 - Increased speed and elbow use associated to higher clinical score
- **Conclusions** – identification of stroke compensations and adaptations in kinematics and brain-related activity. Greater SM1 activation associated to paretic arm movement and most especially in most impaired patients (brain compensation strategies). Relevant use of kinematics and brain parameters that showed good correlation with clinical assessments.

NEXT STEP

Use this methodology in rehabilitation context to evaluate the effects of the different rehabilitation methods and at long term maybe toward the post-stroke recovery (see 9.5. perspectives).

Panel 9

8.4. Thesis experimental contribution key-points



Panel 10

4

PART IV – DISCUSSION & CONCLUSION

Chapter 9: General Discussion

This thesis work aimed to evaluate and better understand the brain and kinematics responses when performing UL proximal functional tasks, and to observe how the task-related brain activity and kinematics are affected by healthy and pathological aging (i.e., through the case of stroke). Maintenance and/or recovery of UL function, in healthy or pathological population, is a major point soliciting neuroplasticity phenomena. Measuring the activity of the major brain regions involved in movement's production (i.e., primary sensorimotor cortex - SM1) allows for a better understanding on how the brain is activated to command the movement and how aging affects it. The following specific objectives form the basis of the thesis project.

The first objective was to develop a suitable methodology to explore the functional UL task-related brain activity and kinematics (Muller et al., 2021, named study 1 in the discussion). This method was developed inside a clinical trial exploring the effects of virtual reality therapy (VRT) and high-definition transcranial direct current stimulation (HD-tDCS) on the UL functional recovery in chronic stroke patients. It was then applied inside experimental studies.

The second objective was to delineate the effects of healthy aging on the related brain activity of UL functional tasks. For achieving this purpose, the second study of this thesis (Muller et al., 2023, named study 2 in the discussion) was built to reveal hemispheric differences of the brain hemodynamic (fNIRS) and electrical (EEG) oscillation patterns in young (18-35 yrs.) and older adults (60-90 yrs.) during two unilateral multi-joint UL movements: one with paced-rhythmed movement (reaching task) and one with speed-accuracy demand (circular steering task). We also explored the aging effect on the relationship between the brain activation lateralization and the motor task performance.

The third objective was to evaluate the effects of pathological aging, and more specially stroke, on the task-related brain activity and kinematics of UL movement (Muller et al., in preparation, named study 3 in the discussion). For achieving this purpose, we conducted a second experimental study comparing a group of chronic stroke patients with the group of healthy older adults of the study 2 in order to differentiate the EEG and fNIRS responses over bilateral SM1 regions during unilateral proximal UL movements.

Overall results of these studies offer a better understanding of the task-related SM1 activity and the kinematics of two types of unilateral proximal UL movements. They help to better characterize both the brain and the movement adaptations and compensations that operates to realize a UL functional task with speed and accuracy objectives. Knowing these

mechanisms could latter help to a better maintenance of functional abilities in neurological healthy aging and a better guidance of the post-stroke rehabilitation.

9.1. Task-related brain activity and kinematics evaluation

One main objective of this thesis was to develop a suitable and flexible methodology to evaluate task-related brain activity during functional proximal UL movement.

Neuroimaging methods

Let's first look to the functional neuroimaging methods selection and their suitability in the recording of brain activity during a proximal functional UL movement. The use of fNIRS to identify UL compensation and non-use in stroke population has already been proposed by our team (Bakhti et al., 2016). We suggested the use of a wired fNIRS system with optical fiber-based optodes (oxymon, Artinis) during the kinematics measure of a reaching task. In this thesis, we proposed to use a portable wireless and fibreless fNIRS device (octamon +, Artinis) and to implement a second neuroimaging method to improve spatiotemporal accuracy.

Going back to the neurovascular coupling (NVC), we presented in the introduction that it is a major phenomenon for a good understanding of the brain functioning. Nevertheless, we also stated that integrating complementary sources of information about neural activity can significantly increase the overall amount of information extracted. In that direction, combined EEG-fNIRS has been showed as relevant to elucidate NVC process in humans (Chiarelli et al., 2017). Indeed, both neural signals can be easily recorded simultaneously and there is no influence of these methods on each other. A combined measurement can thus give useful information about electrical and hemodynamic activities at a better resolution during a functional task (Yeung et al., 2022; Li et al., 2022). From a methodological point of view, surface EEG has lower spatial resolution and higher temporal resolution while fNIRS offers better spatial resolution but a poorer temporal resolution (Parasuraman & Caggiano, 2005). Both methods can thus overcome each other limitations. Additionally, EEG and fNIRS signals are associated with the neuronal electrical activity and hemodynamic responses, respectively, providing a built-in validation for identified activity and full picture of the NVC.

In both experimental studies performed during this thesis, we confirmed that fNIRS and EEG signals were giving complementary information related to functional activity of the brain during UL movements (Chiarelli et al., 2017). For example, in the healthy aging study (study 2) we did not find an age-related effect on the laterality of fNIRS-amplitude in the sensorimotor

network, but we did find age effects on the response time of the hemodynamic response. In the same study, EEG results provided differences in brain asymmetry and on the ability to modify excitatory-inhibitory capacity in the sensorimotor network. Thus, all these findings bring out specific patterns of the brain functioning with aging. In the stroke part (study 3), we found effects of both neuroimaging methods to identify brain modification with for example higher fNIRS activity and lower EEG-ERD for the reaching task. Moreover, the complementary effect of both methods was shown in both experimental studies (studies 2 and 3) with different effects of age x hemisphere interaction. For the healthy aging part, we found an interaction of age by brain laterality only in EEG signals and not in fNIRS ones. This difference could be due to the fundamental differences of the underlying mechanisms between electrical and hemodynamic signals. Indeed, EEG is able to differentiate excitatory and inhibitory activity, but it is not the case for the hemodynamic response as revealed by fNIRS (Klimesch et al., 2007; Zich et al., 2017). In another hand, fNIRS could overcome the EEG limits. Indeed, EEG is recorded responses of more widespread areas than fNIRS, that could lead to spatial differentiation difficulties (Nirkko et al., 2001).

Both methods were also able to provide related information. For example, in study 3, we found that more engagement of neural tissues (i.e., stronger EEG-ERD and higher peak in fNIRS) was associated to a higher deficit (i.e., lower score at the FM-UE). In summary, this synchronous recording allows a complementary and associated vision of the brain activity when moving UL.

Even if the analysis methods selected in the present studies were not providing information about connectivity (i.e., studying the brain neural connection on a huge temporal and spatial scale, (Koenig et al., 2005), we were able, with primary analyses of brain signals collected at the scalp levels, to discern effects of aging. Another major benefit of the use of these methods in the context of movement is to uncover the ‘dialogue’ between the central command (i.e., brain activity as reflected in the NVC) and the output (i.e., kinematics of the movement). For example, in another context, the study of Delcamp et al. (2022) showed a relationship between alteration of functional cortico-muscular connectivity (i.e., EEG-EMG coherence) and motor function decrease through elbow extension tasks in chronic stroke population. Our results on 3 various population (21 young, 21 old healthy, 21 stroke) reinforce the interest for the integration of these two neuroimaging methods for monitoring the brain hemodynamic and electrical activity in healthy adults and patients during UL functional tasks (paced-reaching, circular steering, see Li et al., 2022 and Yeung et Chu , 2022, for reviews).

Kinematics evaluation

Besides, we wanted to choose and develop functional proximal UL tasks that could provide relevant kinematics parameters to understand the movement reorganization (i.e., compensations, movement time, accuracy, speed, performance, ...). There was a lack in the literature at this level, since most of the research projects on task-related brain activity were looking for distal tasks or tasks not using full UL (i.e., from trunk to wrist). Since full mobility of the UL is necessary in everyday life activities, it was applicable to use standardized UL movement tasks such as reaching tasks and circular trajectory tracking tasks.

What is thought interesting with the tasks selected, is that we provided to participants one task where the aim is to go at their own maximal performance (i.e., circular steering task) and one that is paced and consequently more standardised for the strategies adopted (i.e., reaching task, with movement rhythm constraint). The choice of both tasks was based on one main criteria: reproduce movements necessitating the use of all the UL joints, that could be involved in everyday life UL tasks (reaching objects, getting dressed, moving with speed and accuracy). Evaluation of these two tasks is interesting, as most of the movements proposed in the literature are either isolating one joints, either studying more distal movements. Moreover, the compensation of the trunk during UL movement is likely to be identified in proximal tasks. The added value of integrating a circular steering task to the reaching task was to go to the integration of speed-accuracy strategies (Fitts law, Fitts, 1954).

Looking more specially in the stroke population, the use of a Kinect to evaluate UL non-use appears a good method. Indeed, as developed and validated in a previous thesis work (PhD of K. Bakhti), the assessments of the UL non-use with a Kinect were shown to be relevant in stroke population. The use of Kinect is easy and accessible for many clinicians (Bakhti et al., 2018) and was well validated for ecological reaching movement (Faity et al., 2022). Indeed, as it is marker-free, it appears a really good tool to calculate new clinical scores such as PANU that quantifies the amount of proximal non-use of the upper limb. Moreover, the software developed for the circular steering task is also quite easy to use and is providing real time information about the speed (time per laps) and accuracy (bias and % out). In our research work, the use of kinematics variables has been able to properly detail arm movement organisation and strategies to realize the specific chosen tasks. Adding performance scores in this context of compensation provided added value for the results as it could lead to a good identification of the importance of the trunk use to achieve high level demanding task (i.e., circular steering task). In stroke population, the development of compensatory strategies is a usual response to

UL deficit (Taub et al., 2013). Mostly, we can observe an excessive use of trunk flexion when reaching with paretic UL (Cirstea & Levin, 2000; Roby-Brami et al., 2003). This trunk excessive flexion is associated to a reduction of the range of elbow extension and shoulder adduction (Faity et al., 2022). In the last experimental study (study 3), we found that an increased use of elbow extension and speed of the hand on the reaching task were associated to lower motor deficit and higher function (i.e., higher clinical scores at the WMFT and FM-UE). This result is making sense with previous literature around kinematics and clinical scores saying that they could be correlated (Van Dokkum et al., 2014) but that this correlation is altered by the ceiling effects of the clinical scores (Schwarz et al., 2019).

Thus, associated to clinical evaluation, the use of kinematic recording during functional tasks could help to have a better view of the patient evolution, going deeper in understanding how the patient is doing the movement. Thanks to this kinematics evaluation of movement, we can more specifically know what is not correctly functioning and in turn, target the rehabilitation programs with more precise objectives (i.e., increase elbow angle, decrease trunk movements, increase speed, ...). Kinematic recording is also helpful in characterizing the occurrence of non-mandatory compensation, for example by using the PANU evaluation, to have a better guidance of post-stroke rehabilitation with objective parameters to work on.

In the field of healthy aging, this kind of movement evaluation can also be interesting as we know that functional movements involving proximal UL joints (e.g., shoulder, elbow) are affected and could present modification in the speed and accuracy components of the movement (Wittenberg et al., 2022). Thus, the use of kinematic analysis appears useful to determine the modifications of movement strategies and may help acting to prevent from functional decrease (see section “going to an even more healthy aging”).

To sum up these methodological aspects, by using different tasks and different neuroimaging methods we proposed a complementary evaluation platform of the possible effects of both healthy and pathological aging on the brain activity when moving. The selection of two functional tasks, different in their level of demand, allow for a better report of the effects of healthy aging (i.e., using the circular task was more discriminating) and stroke (i.e., reaching task already provides information related to the pathology and circular task completes it). Moreover, in the study 2, we found that EEG was more sensitive to differentiate the healthy aging brain, whereas with study 3 we found that fNIRS was providing, as EEG, clear information on the brain reorganization following a stroke.

To finish with practical implications, we proposed methods that are easy and quick to use in rehabilitation context that could completely be done as a routine evaluation. Indeed, the time to setup both EEG-fNIRS systems is about 10 minutes (i.e., for a trained person, the training can be done in 1h) and the kinematic part does not need much time (except the 2 min to turn on the computer and Kinect). Moreover, with the development of automatized scripts for the extraction of the parameters of the movement and brain, it is at the end, not time consuming.

9.2. UL movement strategies and compensation

Aging and the onset of disease are characterized by a general decline in physiological functions and behavioural abilities (Spirduso & Asplund, 1995), that are leading to detriments in the behavioural capacity of activities of daily living (Hicks et al., 2012).

Looking first to the effect of healthy aging on the selected proximal UL movements, we found that the kinematics strategies to do the tasks were similar for both age groups. This highlights the high function level of our population, which we will return later. The only movement parameter that was negatively impacted in aging was the performance in the circular steering task (IPe, due to a decrease speed, study 2). Nevertheless, this modification makes sense as there is a slowing of motor activities (bradykinesia) typically occurring with advancing age (Salthouse, 2009). Consequently, for healthy older adults, the circular steering task was more sensitive to detect these speed modifications; this is likely due to the increased difficulty of this task in comparison to the paced-reaching task that was not requiring important mental and physical resources. We also observed that despite poorer performances, the healthy old adults did not use trunk compensation to realise any of the tasks which was a strategy adopted mainly by stroke patients.

As described in previous section (i.e., *Task-related brain activity and kinematics evaluation*), stroke population is likely more susceptible to present compensatory strategies to realize UL movement. These compensations can be “mandatory” (patients have no choice and cannot do it another way) or due to proximal-arm non-use (patients can modify trunk compensation to improve the quality and efficiency of their movements). The compensation evaluation was already presented in the literature (i.e., PANU assessment, Bakhti et al., 2017). However, we provided here new information about the use of the trunk compensation in spontaneous condition during more difficult task (i.e., circular steering task) as compared with

a “normal” healthy movement. We were able to demonstrate trunk compensation for both UL tasks (see section 4.1. *Tasks performance and kinematics* of study 3). In the literature, these trunk compensations strategies have been proposed to describe the rehabilitation trajectories during the recovery phase after stroke. Indeed, even if they can limit the recovery of more-normal movements and more-functional use of the paretic upper limb depending on the impairment severity, one can imagine that they can precede the recovery of more-normal movements (see perspectives part in chapter 10, and for a review see Jones, 2017).

Looking to the performance of the tasks for the stroke population, our results are in line with previous works showing a clear performance decrease when using paretic UL in unilateral movements (Nakayama et al., 1994; for our results see section 4.1. *Tasks performance and kinematics* of study 3). We nevertheless can discuss the fact that, in our stroke population, most of the patient’s paretic arm was their past non-dominant hand (14/21 kept their dominant hand from before the stroke). In the literature, while some studies observed better functional and strength gains in the dominant arm after therapy (Walker et al., 2005), and thus less motor impairment in participants whose paretic arm was previously dominant (Harris & Eng, 2006; Waller & Whitall, 2005), other research has reported little difference in motor and functional recovery dependant on the previous laterality (Langan & van Donkelaar, 2008). However, as the tasks proposed are not requiring a huge distal fine motor control, the dominance before stroke could be likely less impacting. Finally, looking to the performance score of the circular steering task (I_{Pe}), the fact that both arms performances were lower in the stroke patients, makes sense because it has been previously shown that damage to a single hemisphere produced deficits in both the contralesional and the ipsilesional arms (Metrot et al., 2013). Thus, the performance of the non-paretic hand could be lower than the dominant hand of a healthy elderly.

Going to the hand dominance in healthy aging (study 2), despite lower performances (I_{Pe}), their hand dominance was preserved with significant advantages of the dominant hand over the non-dominant hand as observed for the young subjects (see figure 2 of the study 2). This is in line with previous studies indicating that older subjects showed more often strongly lateralized behaviour specially with the right hand (Dittmar, 2002; Bernard & Seidler, 2012).

In this section, we highlighted the compensation and strategies of UL movement to deal with functional decrease in both populations. Despite poorer performances in the circular steering task, healthy old adults seemed to privilege similar movement strategies as young adults. We can nevertheless hypothesise that this could be due to the physical activity/fitness level of our group (see section “going to an even more healthy aging” for more details). It could

in fact have had an influence on the physical performances that were close to the young group. In another hand, the stroke subjects presented reduced performances with modified strategies of movement. Motor adaptation enables the nervous system to accommodate for changes in the body or environment that would otherwise produce errors and jeopardize task performance (Krakauer et al., 2019). Our results are in accordance with the literature showing the relationships between motor adaptation, motor impairment, and functional independence (in elbow force production, Hardwick et al., 2017; reaching task, Schweighofer et al., 2018; motor learning Wadden et al., 2017).

9.3. Brain compensation in healthy and stroke aging

Starting with healthy aging brain reorganisation (study 2), we must keep in mind that, as mentioned in previous section, our healthy old population was rather active. There is considerable evidence that chronic physical activity positively impacts brain health and function (Singh & Staines, 2015). This could be a real explanation of the absence of main age effect on brain changes during the reaching task we expected to observe based on the literature (Larivière et al., 2019). This task was, as commented before, not able to discriminate older and younger subjects. This was not the same for the circular steering task. Indeed, this task allowed to identify compensation phenomena as identifying a higher recruitment of the neural pathways in the ipsilateral hemisphere compared to the young subjects to reach their own maximal performance.

Going to stroke population (study 3), we have to look to the story in the other direction. Indeed, the reaching task, that is already more demanding for the stroke patients (i.e., occurrence of compensation to reach the ball), leads to brain activity modification with greater fNIRS bilateral activity, and a tendency to lower movement desynchronization in comparison to healthy old adults. This might also suggest that patients developed brain compensation to reach the demand of such a task, and deal with the use of a supplementary joint / muscle group to do it (i.e., trunk muscles). For the circular steering task, we can hypothesis that the absence of brain modification in the stroke patients can be explained with the results of the second study. Indeed, we found that healthy older adults were already presented brain compensation with a bilateral SM1 recruitment on this task. Moreover, the brain activity over SM1 is likely reaching a plateau and there is certainly other brain region reorganization that could have been observed such as frontal areas to deal with visuo-motor information (Sakurada et al., 2018). Since our

system did not allow us to record brain activity in these regions, we could not observe these phenomena.

The nature of the tasks explored, the paced-reaching task that is discrete with loose time-accuracy constraint and the circular steering task which is continuous with high speed-accuracy constraints, could explain the bilateral SM1 pattern observed in healthy and pathological older patients in the circular steering task. The proximal nature of the UL movement (mainly involving the elbow and shoulder joints) and the speed requirement to perform the task already reduce any asymmetry of lateralised sensorimotor network activation because the elbow and shoulder joints classically involve more ipsilateral activations than distal movements (Nirkko et al., 2001). Even though it would require more cognitive resources, such as attention and visual-motor coordination, the final motor output from the sensorimotor regions measured using the fNIRS/EEG neuroimaging methods showed a relative bi-hemispheric activation pattern for healthy and stroke older adults.

We can also question the localisation of the brain activity and possible brain reorganisation besides the SM1 ones. Indeed, the morphology of neurons in the PFC (pre-frontal cortex) is more susceptible to present age-related change, insofar these cells show a decrease in dendritic branching in rats and humans (Burke & Barnes, 2006). Because the hippocampus and the PFC are particularly vulnerable to the aging process, it is not surprising that performance on tasks that require information processing in these brain regions declines with age. In the present work, we just recorded the activity of the SM1 thus, possibly some reorganizations were not evaluated. This is especially true for the circular task inducing visuo-motor feedback, and thus, probably, PFC activation. Nevertheless, regarding the reaching task, the brain age-related reorganisation showed hyper-activity for stroke patients, thus, supported the fact that a few activations were still passing through the motor cortices. More research will be nevertheless needed, to better understand and characterize the reorganisation located on the motor and frontal areas of the brain. Indeed, motor tasks are distinguished based on their profile of activation across elements of the central motor network (Roland & Zilles, 1996). These profiles seem plausible in view of previous studies showing that movement-related activation depends on task properties other than mechanical features (Dassonville et al., 1998; Jäncke et al., 2000; Krings et al., 2000). Hence, the reorganization we observed can just apply to the specific movements we analysed.

If we try now to link our results to the literature models of cognitive aging, we can go back to the CRUNCH model (compensation when facing elevated task requirements with a

higher recruitment in the opposite hemisphere, Reuter-Lorenz & Cappell, 2008). Consistent with the compensation hypothesis, our results suggest that older adults and stroke adults recruited a similar network as healthy adults but used it inefficiently in the circular steering task (see figures 2 and 3 in studies 2 and 3). Whereas, in the reaching task healthy older adults counteracted age-related neural decline through a plastic reorganization of neurocognitive networks and presented a similar brain activation (see figure 3 and 4 of the study 2). For the stroke population, nevertheless, we did find a significant difference in movement and brain-related activity compared with healthy older adults, supporting the effects of stroke, and not just aging (i.e., chronological age of our subjects) on the brain compensation and lack of differentiation following a stroke (see figure 3 and 4 of the study 3).

In stroke population, we can also look to the models of functional recovery present in the literature and how plasticity reorganisation is viewed in association to functional recovery. We can first mention the interhemispheric competition, which is the idea of a reduced excitability of the lesioned M1 primary motor cortex (Murase et al., 2004) and an increase excitability in the contralateral non-lesioned one, increasing its inhibitor effect on the ipsilesional functional circuits. Moreover, we can discuss the vicariance model, which consists in the substitution ability of the non-lesioned hemisphere that will take in charge the function of the lesioned one (Finger, 2009). A last model tried to explain the role of the lesioned hemisphere regarding the “ipsilesional structural reserve” which measures the lesioned motor cortex ability to assume motor functions (Bimodal Balance Recovery Model, Di Pino et al., 2014). All models are following the same idea: with functional rehabilitation, the plastic reorganization will lead to adaptative compensatory phenomena in both lesioned and non-lesioned hemispheres (Berthoz & Weiss, 2017). In other words, practice can drive sufficient reorganization of neural connectivity in surviving brain regions to permit a degree of vicariance (take-over) of the original function of these regions (see Jones, 2017 for a review around post-stroke plasticity).

The choice of functional neuroimaging methods with a low number of channels was relevant enough for this project as it is more convenient to transfer it in rehabilitation units. However, we can complete this section by mentioning the necessity to study functional connectivity changes with aging and/or stroke (i.e., temporal correlation of spontaneous activity between different areas, Baldassarre et al., 2016). If we consider the brain functional connectivity in healthy aging, a review suggested that the change in functional connectivity with aging is related to cognitive decline as presented in the introduction (Damoiseaux, 2017).

Looking to pathological aging, studies have shown that motor network connectivity undergoes reorganisation during functional recovery from a stroke, that can be related to behavioural recovery (Desowska & Turner, 2019). These authors indicated that an increase in functional connectivity is related to an increase of functional motor gains. Finally, another study has shown, in stroke chronic stage, that a higher interhemispheric functional connectivity in M1 was associated to well recovered motor function, suggesting compensation mechanisms (Liu et al., 2015). Nevertheless, the study of functional connectivity has to go through the use of more complex neuroimaging analysis using fMRI for example (reducing the possibility of movement) or the use of more channels with fNIRS (Vergotte et al., 2018) and EEG, reducing the feasibility in rehabilitation routine.

Looking to our results and the literature, we highlighted brain reorganisation related to state modification (i.e., aging, stroke) that seems to be associated to compensation, in the modification of specialization of brain hemispheres (i.e., loss of de-differentiation in both types of aging, healthy - Li & Lindenberger 1999; and pathological with the case of stroke – Schaefer et al., 2007), and in modification of functioning of the contralesional hemisphere to the movement.

9.4. Going to an even more healthy aging

If we go back to the third aging paths presented by Claude Jeandel, the optimum point to reach is the aging at high level of function. This path is representing a robust aging, characterized by the maintenance of functional capacities or their very moderate impairment. This notion has been addressed in the review of Khan and colleagues (2017). This review presents a way of measuring aging by using a score to integrate the differential trajectories of age-related decline that individuals with the same chronological age can have. Indeed, lots of studies highlighted the fact that chronological age offers limited information regarding the complex processes driving biological aging (Marioni et al., 2015; Weidner & Wagner, 2014; for a review see Khan et al., 2017). The idea driven by this biological aging is that the life trajectories (i.e., lifestyle, environmental factors, epigenetic, disease, ...) have to be included in the evaluation of the biological age. And thus, a person can present a normal aging (i.e., his/her biological age is equal to his/her chronological age), an accelerate aging (i.e., his/her biological age is superior to his/her chronological age), or a super aging (i.e., his/her biological age is

inferior to his/her chronological age). These three paths of aging are presented in figure 20 (from the review of Khan et al., 2017).

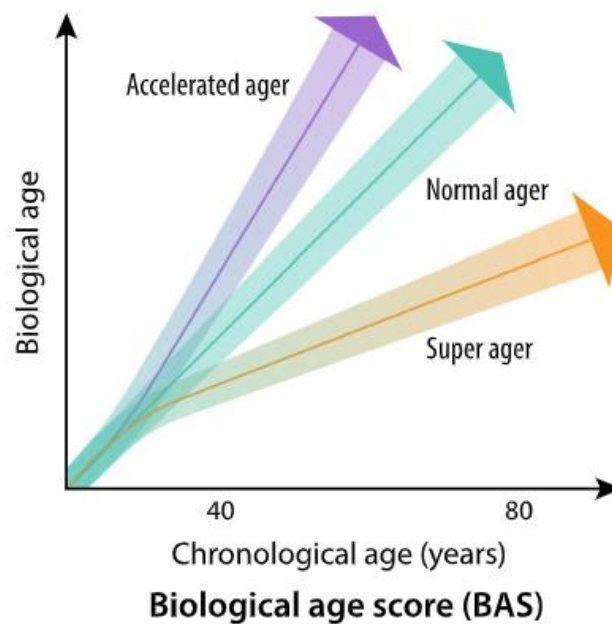


Figure 20 - Aging trajectories.

Model and figure proposed by Khan et al. (2017)

Looking to the WHO recommendations (e.g., 50 to 300 minutes per week of moderate intensity endurance activity ; or at least 75 to 150 minutes of sustained intensity endurance activity) and definitions around so-called “healthy aging”, such state is related to a process leading to wellbeing (i.e., “developing and maintaining functional ability that enables wellbeing in older age”, Michel & Sadana, 2017). It is then important to not only seeing on one hand healthy aging and on the other hand pathological aging. Indeed, healthy aging is more tending to a maintenance of abilities and states that is higher than what could be expected at a given age.

With these notions, let’s now look to what could help to lead to this robust/ super aging. Most of the papers studying aging, use the notion of quality of life. Quality of life implies for the individual the ability to perform certain simple or elaborate acts that require the recruitment and coordination of several functions. The functional approach is therefore relevant to distinguish the different modalities of advancing age. Above all, it integrates the notion of reversibility or plasticity, which accounts for the possibility of changing trajectory under the effect of adapted actions. Thus, the heterogeneity of aging is induced by what every individual is doing in his/her life. Indeed, the stimulation of neuroplasticity would depend on the different activities undertaken during the individual's lifetime (Phillips, 2017; Reuter-Lorenz & Park,

2014). The stimulation generated by the social, intellectual, or else physical activities is contributing to the development and maintenance of cerebral structures, via the experience-dependant plasticity (May, 2011).

This relationship between cognitive aging (deterioration of capacities), motor learning (the process of acquiring or consolidating new or learned skills) and neural plasticity has been reported in a review of Cai and colleagues (2014, see figure 21). Interactions of cognitive aging, experiences, environments, and brain development collectively contribute to the observed discrepancies in motor and cognitive functions between younger and older. This model shows that for a successful aging, cognitive and motor training are essential to stimulate neuroplasticity and even more for high functional risk adults.

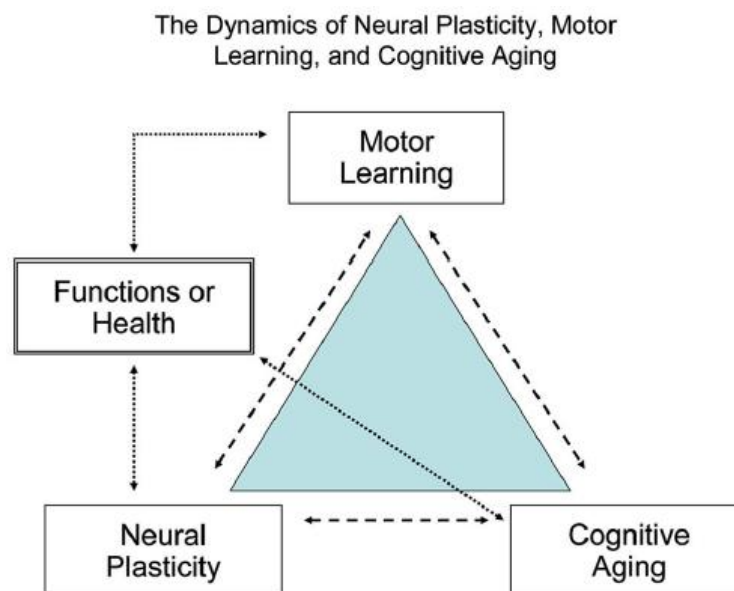


Figure 21 - Relationship between brain plasticity, motor learning and cognitive aging.

Motor learning and practice are leading to increase neural plasticity and then to a maximization of motor function (i.e., quality of life). *Figure from Cai et al., 2014*

In this context we can mention the research around physical activity. Since the nineties, lots of studies have shown how exercise and motor practice could improve neurocognitive function and thus wellness in older adults (Albinet et al., 2014; Studenski et al., 2006).

If we look to the results found in this PhD thesis, we did not find such major differences in the task achieved. Indeed, for example in the reaching task, the kinematics was not significantly different between young and older subjects. In the circular steering task for older, the performance was lower, but the hand laterality and kinematics (i.e., use of elbow, shoulder and trunk) were similar as the younger subjects. It is here important to precise that this lack of effects could be explained by the level of activity of our old subjects. Indeed, according to

informal discussions and exchanges with the participants, we found that they were for all, either still having an activity (i.e., working, involved in an association) either following weekly or daily physical activity (i.e., walking every day, practicing bike, dance, ...). Thus, we can hypothesize that our subjects were closer to a robust aging than a classical one. This can also reinforce the importance of maintaining activities to stimulate the brain and by extension, the functions. Nevertheless, this hypothesis may have needed more objectives measures of physical activities to reinforce it (e.g., GPAQ of the WHO, Armstrong & Bull, 2006; IPAQ, Hagströmer et al., 2006).

We can imagine that the proposed functional task-related brain activity evaluation could be used to follow the evolution of healthy aging, through movement and brain reorganisation. With this idea, we could possibly guide the management of aging, orienting elderly to physical activity for example. Finally, we can talk about prevention and most specially about primary prevention. The primary prevention is aiming to reduce the incidence of a disease or health problem, thus reducing the occurrence of new cases in a healthy population by reducing the causes and risk factors (WHO). The idea is to act before any additional troubles and in the context of aging, not going to pathological aging, but also going to an even more healthy aging. It is, indeed, an important part of the preservation of the UL function or at least to delay the functional decrease. In this context, the methodology we proposed offers an objective evaluation of movement and brain markers that are affected with aging. Their use to follow healthy aging could help to avoid the displacement to a pathological aging with for example an alert to follow the physical practice recommendations of the WHO.

9.5. Perspectives for post-stroke rehabilitation

The complexity in this part will be to really differentiate which reduction of function comes from the physiological aging, and which one results from the pathological post-stroke deficiencies. This point underlines the importance to differentiate the management of care when facing a young post-stroke adult and an older one.

Literature has shown that functioning and disability after stroke are strictly related not only to the disease but also to the presence or absence of environmental facilitators that increase persons' performance and social participation (Cerniauskaite et al., 2012; Rochette, 2001; for a review on the link between personal factor and post-stroke participation see Della Vecchia et al., 2021).

Looking forward, with more results about this task-related brain activity inside a stroke rehabilitation, we can think about some perspectives for the orientation and individualization of the rehabilitation. Let's think about an orientation of care based on the arm-use (which is the major goal in stroke rehabilitation and can be evaluated during both tasks of our experiments) and the brain related activity (*is the lesioned hemisphere activated? is the contralesional hemisphere activated for paretic movement?*). Regarding the avenues of patient management according to the results obtained during this dual cerebral and functional assessment, we already know the modalities of management in cases where the arm-use is too low (Bakhti et al., 2017, 2018). The goal for these patients is to increase the use of their paretic arm and decrease their non-mandatory trunk compensations. Concerning cerebral lateralization (based on IL indicator), during the reaching task, if it traduced a more contralesional activity with a trunk compensation, it could be considered to guide the patient towards a non-invasive transcranial stimulation (e.g., HD-tDCS) of the ipsilesional hemisphere to the paretic arm in order to stimulate the neuroplasticity potential and to counteract the inter-hemispheric imbalance (Flöel, 2014; Teo et al., 2016). Thus, this would result in increased ipsilesional activation leading to increased use of the paretic arm (Chhatbar et al., 2016) and reduced contralesional activation leading to a decrease in trunk use (Bani-Ahmed & Cirstea, 2020). A recent work has demonstrated the potential of tDCS as non-invasive brain stimulation technique to positively enhance interactions between the two healthy hemispheres (Cabibel et al., 2018). Administered to the injured motor cortex, contralateral to the paretic arm, it highly suspected to promote brain plasticity (Schlaug et al., 2008).

One of the major interests of the task-related brain and kinematics evaluation, is that we can have information on the central command and on the output at the peripheral level. We can then play with bottom-up (e.g., VRT) and top-down (e.g., tDCS) rehabilitation methods to improve UL paretic arm function.

Nowadays, fNIRS and EEG methods have been used in several stroke studies (Huo et al., 2021). Nevertheless, their application to oriented rehabilitation methods are still difficult and unclear while our findings come to reinforce their interest, especially when associated to functional evaluation.

The stimulation of brain plasticity appears to be the solution to the UL function alteration whether we are on a pathological context or not. That could be induced thanks to experience-dependant response by proposing to the subjects' physical activities programs, VRT, non-invasive brain stimulation, combined methods, motor imagery, or else.... Figure 22

is presenting an illustration of what could be the association between the level of UL functional recovery and the neuroplasticity stimulation. The goal here, is thus the individualization of rehabilitation to find the most efficient methods for each patient that will lead to the highest recovery.

Finally, to echo to the healthy aging part, we can also in the context of stroke talking about prevention, with tertiary prevention. Tertiary prevention refers to all the means implemented to avoid the occurrence of complications and relapses of diseases (WHO). Most of all, in this context, prevention is mandatory to anticipate the effects of aging that could be exaggerated with deficiency related to pathology. Here we proposed a new way to individualize the management of care and rehabilitation by focusing at the same time on the function and on the brain plasticity. Both are related and, studied together they could help to lead to a better orientation of individual rehabilitation and work as a preventive tool to avoid complication and facilitate the life with the pathology.

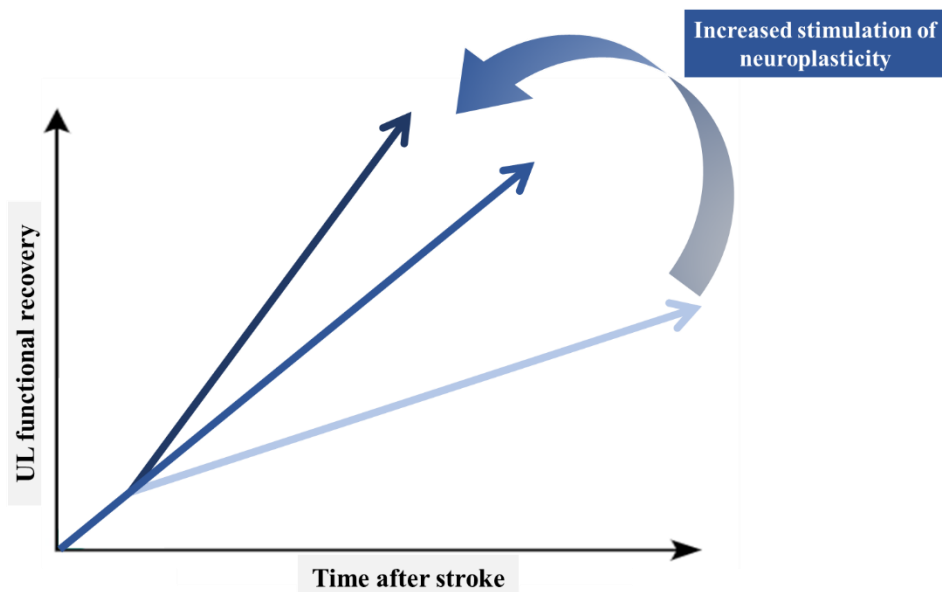


Figure 22 - UL recovery following promotion of neuroplasticity during post-stroke rehabilitation.

The different trajectories could represent the potential of recovery following the use of different rehabilitation methods, each patient is different, and the individualization of the rehabilitation program is a major point to increase the potential of recovery using the adapted methods.

9.6. Limits

In this section we will not come back to the specific limits of the three studies. They can be found in the dedicated section of all three articles.

The major limit we can see to this work is the fact that we are not seeing the ‘real’ brain activity reorganisation whether it is with healthy or pathological aging. Indeed, with the few numbers of channels used (i.e., 8 in EEG and 8 in fNIRS) and their location (i.e., only above SM1), we were just able to identify functional cortical activity in the motor areas. Moreover, we know that in both kind of aging there are neural reorganisation that might lead to the use of supplementary neural pathways to accomplish demanding tasks. Nevertheless, the choice of limited channels was justified regarding the final perspective of this work: to demonstrate the possibility to use of such neuroimaging methods in rehabilitation context and during rehabilitation phases. For this purpose, the use of a light neuroimaging tool was made to develop a method easy to transfer and use in rehabilitation. However, we can suppose that implementing more channels and covering more brain areas could have led to supplementary and more generalizable results.

Another limit we can discuss is the choice of the analysis method for the brain signals. Even if we based our choices in similar studies (for fNIRS, Delorme et al., 2019; Besson et al., 2019; for EEG, Nakayashiki et al., 2014), recent advances in the field of functional neuroimaging analysis give new recommendations for analysing simultaneous fNIRS-EEG signals (Yeung and Chu, 2022). In their review, the authors recommend the use of correction methods to lead to less data loss during the artifact removal process, and the use of clustering channels methods.

In another hand, looking to the selected tasks, the reaching task could present a major limitation as it was paced with the same rhythm for every participant. Such constraint around the speed of movement could have led to increased use of compensation in stroke patients to reach the ball at the required speed. For the circular steering task, the instructions given were leading to an orientation of the task with speed and less accuracy. Maybe, some subjects would have been more comfortable with less speed and accuracy and that would have led also to a compensation reduction. Nevertheless, as the performance index use on this task is integrating speed and accuracy, the performance would not have been modified (see section *More information about kinematics* for more details about the IPe calculation).

Chapter 10: Conclusions and perspectives

This PhD thesis work aimed to develop first a methodology to evaluate the kinematics and brain-related activity to unilateral proximal UL movement. The main objective was to assess both brain and movement adaptation and compensation strategies associated to aging and more specially to healthy aging and pathological one through stroke case study. We identified two basic functional tasks that were relevant enough to describe movement performances and compensations strategies: the paced-reaching task and the circular steering task. In addition, we proposed a simultaneous recording of both SM1 hemispheres using combined fNIRS-EEG neuroimaging. With this framework, we observed movement modification with healthy aging (i.e., performance reduction) and with stroke (i.e., increased use of trunk compensations and reduced speed of movement). Moreover, we observed ipsilateral greater excitatory activity in healthy old adults to reach high demanding level of performance of the circular steering task. This was also true in stroke patients during the reaching task, and most of all for patients with higher UL impairment that need to use more neural resources to realize the reaching movements. These findings help to better understand the neurophysiological modification associated to aging process and stroke UL paresis.

Looking to the perspectives of such work, from an applicative point of view, this thesis work is opening a window on the use of supplementary markers of UL recovery at the level of the movement kinematics (sensor-less motion capture devices) and brain related activity (portable fNIRS and EEG). The first major perspective of this work is to move these methods in rehabilitation setting to better describe concrete markers of recovery over time. Thus, firstly, it will be important implement the proposed methods in the monitoring of the effect of conventional therapy and the effect of other types of therapy (non-invasive brain electrical stimulation, VRT, motor imagery, mirror therapy, ...). If we manage to monitor specific markers from both movement and brain levels, the next step will be to use this methodology to evaluate patients at their entrance in rehabilitation program and to guide them in the more adapted rehabilitation path. The first step in this perspective will be explored in the clinical trial which methodology was presented in the first experimental chapter (ReArm project, Muller et al., 2021).

Considering the case of healthy aging, an interesting perspective of this work could be to explore from a longitudinal point of view the evolution of such movement and brain markers with age. It could thus lead to better information of the time scale of movement and brain

adaptation. Moreover, associated these data with the level of activities could lead to a better understand of the beneficial effects of physical practice on these specific markers.

Another perspective of such a project could be to explore other brain areas to potentially identify other relevant regions that are likely to evolve following age-related UL movement reorganisations. As discussed in studies 2 and 3 and in the limits section, providing information using more channels could benefit as it might allow to identify more brain markers of UL movement. Nevertheless, in this context, a good balance between cost and demand has to be established as the use of more complex neuroimaging systems will also lead to more complicated post-treatment, interpretation and more time to a therapist use.

Looking to the proposed tasks, first looking to recent literature, we can imagine new parameters of movement to analyse. For example, for the circular steering task it could have been interesting to decompose the movement in sub-movements (Guigon, 2021). It has previously been shown that to counteract the increasing noise and decreased perceptual efficiency, older adults were increasing the number of sub-movements (Walker et al., 1995). We can also target next work to other types of tasks going for example to the use of more distal tasks. Indeed, looking to the evolution of patient's characteristics we can clearly see a better recovery at the proximal level and a lower one at distal level. The use of dual motor tasks could also be interesting as it is allowing interaction with daily life environment with for example reaching a door in a standing position.

AGING CONTEXT

↑ Elderly population ↑ Stroke risk ↓ UL function and autonomy
Aim = Increase motor function for a better life at home

↑ UL FUNCTION

Better knowledge of brain-UL function relationship

Neuroimaging methods

- ❑ Easy to use and to combine
- ❑ In ecological condition

More adapted: fNIRS and EEG

UL function evaluation

- ❑ Objective evaluation
- ❑ Easy and quick evaluation

More adapted: Kinematics

TASK-RELATED BRAIN ACTIVITY

Healthy young

- ❑ For unilateral movement, higher activity in contralateral hemisphere

Healthy aging

- ❑ Greater activation of the ipsilateral hemisphere to reach similar levels of performances

Pathological aging (stroke)

- ❑ Different involvement of the healthy hemisphere depending stroke stage

Experimental contribution of this thesis

Methodology

Proximal arm movement strategies
 → Paced-reaching task
 → Circular steering task
 SM1 recording using
 → EEG
 → fNIRS

Healthy aging effects

Kinematics

- Lower performances but hand dominance preserved
- No compensations

Brain

- Ipsilateral higher activity during the circular task in older
- Tendency to lower ERS

Stroke effects

Kinematics

- Trunk compensation
- Reduced speed

Brain

- Greater activation on the reaching task with paretic arm

Relationship between...

- Clinical scores, kinematics parameters and brain activity



Perspectives ?

- ❑ Explore the kinematics and brain-related activity during rehabilitation to assess the effects of the different rehabilitation methods
- ❑ Explore more areas of the brain for example in frontal areas involved in visuo-motor tasks
- ❑ Test older healthy population
- ❑ Explore more distal tasks or dual tasks

Short presentation in French

Effets du vieillissement sain et pathologique sur l'activité cérébrale lors du mouvement du membre supérieur : perspectives pour la rééducation post-AVC

Introduction

La population âgée mondiale augmente plus rapidement qu'auparavant, et, selon l'organisation mondiale de la santé, d'ici 2050, les personnes âgées de 60 ans et plus seront plus nombreuses que les jeunes adolescents-adultes (15-24 ans ; OMS, Vieillesse et santé, 2021). Le vieillissement a un impact sur de nombreuses fonctions telles que les fonctions motrices, les processus sensoriels et cognitifs. En particulier, la diminution des performances motrices avec le vieillissement (Seidler et al., 2010) altère les tâches de la vie quotidienne impliquant des mouvements des membres supérieurs et donc par extension leur autonomie au quotidien (e.g. contrôle de la main pour les tâches d'atteinte ; Wittenberg et al., 2022). Pour limiter les conséquences, et ne pas conduire à une moins bonne qualité de vie, il est nécessaire d'adapter les soins pour prévenir la perte d'autonomie des personnes âgées afin de leur permettre de vivre de manière autonome le plus longtemps et le mieux possible. Ce vieillissement des fonctions motrices et cognitives peut aller jusqu'au vieillissement pathologique (c'est-à-dire une détérioration physique et mentale due à des maladies liées à l'âge, indépendamment des modifications typiques du vieillissement) avec par exemple un risque accru de développer un accident vasculaire cérébral (AVC ; 90% des personnes touchées par un AVC ont 50 ans ou plus et 50% ont plus de 75 ans, Société française neuro-vasculaire).

Avec une prévalence très élevée, l'AVC est la troisième cause de décès et la première cause de handicap acquis chez l'adulte dans les pays développés. Jusqu'à 85 % des personnes ayant subi un AVC présentent une hémiparésie (Jones, 2017), ce qui affecte leur capacité à utiliser leur membre supérieur (MS) dans les activités de la vie quotidienne (van Kordelaar et al., 2012) et peut entraîner un handicap permanent avec des limitations physiques sensori-motrices et fonctionnelles (Cirstea & Levin, 2000 ; Nakayama et al., 1994). La récupération de la fonction motrice du MS est donc un véritable défi en matière de réadaptation.

Après un AVC, au niveau cérébral, il existe une rupture de l'équilibre interhémisphérique conduisant à une sous-utilisation de l'hémisphère lésé. Dans ce cadre, afin d'optimiser la rééducation, il serait intéressant de connaître le plus précisément possible les caractéristiques des activations cérébrales des patients, ainsi que leur évolution dans le temps en examinant l'activité cérébrale fonctionnelle associée à un mouvement du MS. Dans ce contexte, deux méthodes de neuro-imagerie non invasives permettent d'enregistrer l'activité cérébrale en condition écologique : la spectroscopie fonctionnelle dans le proche infrarouge (fNIRS) et l'électroencéphalographie (EEG), respectivement basées sur la réponse hémodynamique et l'activité électrique du cortex. En les associant, elles pourraient conduire à une meilleure analyse spatiotemporelle de l'activité corticale lors du mouvement afin de dévoiler les mécanismes sous-jacents à la récupération de la fonction du MS (Li et al., 2020). Nous disposons néanmoins de peu d'informations sur l'activité cérébrale sensorimotrice lors de tâches fonctionnelles impliquant l'ensemble de la chaîne articulaire du MS. De plus, un aspect important à prendre en compte pourrait être la cinématique du mouvement, afin d'observer la mise en place par

exemple de stratégies de compensations pour la réalisation des mouvements, aspects très importants de la récupération fonctionnelle. La compréhension des corrélats neuronaux liés à la cinématique des mouvements fonctionnels du MS pourrait aider à mieux comprendre comment le vieillissement sain et pathologique.

Ainsi, ce travail de thèse avait pour but principal de mesurer et mieux comprendre l'activité cérébrale et la cinématique liées au mouvement fonctionnel du MS au travers du vieillissement sain et de l'AVC. A long terme, cela pourrait permettre, par exemple, un meilleur suivi des patients lors de la rééducation post-AVC et ainsi améliorer l'individualisation des programmes de rééducation.

Revue de la littérature

Vieillesse

Le vieillissement biologique est un processus multifactoriel et complexe. Il peut être défini comme l'altération progressive des capacités physiques, sensibles et cognitives, liée à une perte de l'intégrité physiologique (López-Otín et al., 2013). Même dans le cas d'un vieillissement sain, avec l'avancée en âge on observe une diminution des fonctions dont une diminution de la fonction motrice du membre supérieur, primordiale dans les activités quotidiennes. De plus, cette avancée en âge conduit à une augmentation du risque de présenter un AVC (Sharrief & Grotta, 2019). Dans le cadre de l'AVC, la parésie, résultant de la perturbation de l'exécution de la commande motrice, est un des principaux déficits, et le symptôme le plus invalidant chez le patient post-AVC. Elle consiste en une incapacité à générer des niveaux de force appropriés et/ou à développer une motricité distale fine pour effectuer des mouvements, indépendamment de la préservation de la capacité à planifier le mouvement (Bourbonnais & Noven, 1989 ; Gracies, 2005). En raison de son implication dans les activités quotidiennes, le déficit moteur du MS, limite l'autonomie des personnes post-AVC dans les activités de la vie quotidienne et peut induire un handicap persistant (Cirstea & Levin, 2000 ; Nakayama et al., 1994). Les patients vont ainsi avoir tendance à mettre en place des compensations non indispensables (i.e., surutilisation de la flexion du tronc), principalement visibles lors de tâches de reaching (i.e., tâches de saisie). Ce phénomène traduit une non-utilisation acquise du bras parétique. Il a notamment été montré que 61% des patients avec un faible déficit moteur, présentaient une non-utilisation du bras qui freine la récupération (Bakhti et al., 2017).

Neuroplasticité et rééducation

L'altération des fonctions motrices du MS précédemment énoncée peut être soit limitée (e.g., dans le cadre d'un vieillissement sain en essayant de passer à un vieillissement sain plus robuste), soit restaurée (e.g., dans le cadre d'un vieillissement pathologique par le biais d'une rééducation). Dans les deux cas, les modifications des fonctions sont possibles grâce aux phénomènes de neuroplasticité. Il s'agit d'un processus qui conduit à une réorganisation au niveau de la fonction et de la structure cérébrale. Cliniquement, cette neuroplasticité est impliquée dans les modifications cérébrales qui apparaissent après des lésions telles qu'un AVC (Masiero & Carraro, 2008) mais aussi dans la vie quotidienne saine avec l'évolution du cerveau et de ses connexions avec l'âge, l'apprentissage et l'expérience (voir Dayan & Cohen, 2011).

Par exemple, dans le cadre de l'AVC, l'amélioration fonctionnelle du MS parétique est associée au réapprentissage moteur et donc à de la neuroplasticité dépendante de l'expérience (Kleim, 2011 ; Murphy & Corbett, 2009). Les stratégies spécifiquement orientées vers la promotion de la plasticité cérébrale doivent donc être renforcées dans la rééducation. Par conséquent, il est important de cibler soigneusement les méthodes qui peuvent avoir le meilleur impact sur la plasticité cérébrale induite par l'AVC, comme la thérapie par la réalité virtuelle (Laffont et al., 2020), la neurostimulation (Flöel, 2014), l'entraînement assisté par robot (Morone et al., 2020), ou encore l'imagerie motrice (López et al., 2019).

Evaluer l'activité cérébrale et la cinématique du mouvement du MS

Nous avons mentionné précédemment le lien étroit entre la neuroplasticité et la récupération fonctionnelle post-AVC. Ainsi, un bon moyen de mieux comprendre la récupération fonctionnelle post-AVC serait d'évaluer en même temps le mouvement fonctionnel et l'activité cérébrale associée. Les mesures de la qualité du mouvement à l'aide de la cinématique sont considérées comme valides et sensibles pour reconnaître les déficiences du MS chez les personnes post-AVC et effectuant des tâches avec le MS (Bakhti et al., 2017 ; Subramanian et al., 2010 ; van Dokkum et al., 2014). Concernant l'enregistrement de l'activité cérébrale, les différentes techniques de neuroimagerie permettent d'identifier les aires cérébrales actives lors de tâches motrices, ainsi que leurs relations. L'activité électrophysiologique révélée par EEG par exemple apporte une information sur l'activité des potentiels post-synaptiques avec une haute résolution temporelle. L'activité hémodynamique tissulaire étudiée par fNIRS renseigne sur la réponse métabolique induite par l'activité neuronale. Ces deux méthodes portables ont été largement utilisées pour étudier l'activité cérébrale pendant des exercices physiques dans des environnements relativement peu contraignants (Li et al., 2022 ; Perrey & Besson, 2018 ; Tan & Le, 2020 ; Yeung & Chu, 2022).

Lien cerveau-mouvement : vieillissement et AVC

Chez les personnes en bonne santé, les changements physiologiques liés à l'âge modifient les circuits neuronaux au niveau structurel et au niveau fonctionnel (Burke & Barnes, 2006). Plusieurs modèles ont émergé dans la littérature pour expliquer ces réorganisations cérébrales régulièrement observées dans le vieillissement sain lors de tâches cognitives et bi-locomotrices. Tout d'abord, le modèle HAROLD (hemispheric asymmetry reduction in older adults) suggère que, pour effectuer une même tâche cognitive, les personnes âgées recrutent davantage de circuits neuronaux dans l'hémisphère opposé (ipsilatéral ; Cabeza, 2002). En addition, le modèle CRUNCH (compensation-related utilization of neural circuits hypothesis) suggère que des ressources neuronales supplémentaires sont recrutées chez les personnes âgées pour tenter de compenser les exigences accrues d'une tâche en raison d'une efficacité neuronale réduite (Reuter-Lorenz & Cappell, 2008). Pour compléter le modèle CRUNCH et expliquer la suractivation présentée, Park et Reuter-Lorenz (2009) ont proposé le modèle STAC (Scaffolding Theory of Aging and Cognition). Ce modèle suppose que les personnes âgées, pour compenser les altérations physiologiques, recrutent des réseaux neuronaux supplémentaires qui vont soutenir, les réseaux devenus moins efficaces.

Si l'on s'intéresse à ces modifications de l'activité cérébrale après un AVC, on peut se référer aux mêmes hypothèses que dans le cas du vieillissement. En effet, la réduction de l'asymétrie hémisphérique peut faciliter la récupération après une lésion cérébrale. Au stade précoce de l'AVC, l'activation de l'hémisphère controlésionnel pour les mouvements du bras parétique pourrait résulter d'une perte d'inhibition de l'hémisphère lésé sur l'hémisphère non-lésé (Calautti & Baron, 2003 ; Grefkes et al., 2008). Une hypothèse alternative est qu'on fait face à un phénomène de recrutement des aires sensorimotrices controlésionnelles pour faire face au manque d'activation de l'hémisphère lésé (Calautti & Baron, 2003 ; Rehme et al., 2012). On retrouve ici la même explication que pour la modification de l'activité cérébrale liée à la tâche du vieillissement sain : perte de spécialisation et/ou compensation. Ainsi cette balance inter-hémisphérique est considéré par de nombreux auteurs comme un marqueur potentiel de la récupération dans les études de neuroimagerie fonctionnelle de l'AVC (Cramer et al., 1997).

Que ce soit du côté du vieillissement sain ou de l'AVC, peu d'études ont observé ces réorganisations lors de mouvement globaux du MS, tels qu'ils sont réalisés dans la vie quotidienne. De plus, il apparaîtrait intéressant d'associer à ces enregistrements des informations sur la cinématique du mouvement, afin de mieux comprendre le lien entre les réorganisations fonctionnelles et celles cérébrales.

Objectifs

Par conséquent, ce travail de thèse s'est articulé autour de trois objectifs principaux. Le premier objectif était de développer une méthodologie complète pour évaluer la fonction du MS à l'aide de mesures simultanées de l'activité cérébrale et de la cinématique associées à des tâches fonctionnelles. Le deuxième objectif était de délimiter les effets du vieillissement sain sur l'activité cérébrale liée aux tâches fonctionnelles du MS. Enfin, le troisième objectif était d'évaluer les effets de l'AVC sur l'activité cérébrale liée aux tâches fonctionnelles.

Contributions personnelles

*Méthodologie : Enregistrer le mouvement fonctionnel et l'activité cérébrale associée*¹

L'objectif de cette première partie était de développer une méthodologie pour évaluer conjointement, la cinématique de deux tâches fonctionnelles du MS et l'activité cérébrale des régions sensorimotrices primaires (SM1). La première tâche réalisée par les participants était une tâche d'atteinte. L'objectif était d'atteindre une cible (représentée par une balle) en tendant le bras vers l'avant. La tâche était réalisée dans une condition spontanée puis dans une condition d'utilisation forcée du bras (tronc légèrement maintenu sur le dossier de la chaise). La seconde tâche était une tâche de suivi de trajectoire circulaire, où les participants devaient déplacer une souris aussi vite que possible, sur une tablette graphique, en restant à l'intérieur d'une cible circulaire projetée sur un écran. Pour chaque tâche, trois blocs de 20 secondes (suivis de 20 secondes de repos) étaient réalisés pour chaque condition et bras. La vitesse de la main, la

¹ Muller, C. O., Muthalib, M., Mottet, D., Perrey, S., Dray, G., Delorme, M., Duflos, C., Froger, J., Xu, B., Faity, G., Pla, S., Jean, P., Laffont, I., & Bakhti, K. K. A. (2021). Recovering arm function in chronic stroke patients using combined anodal HD-tDCS and virtual reality therapy (ReArm): A study protocol for a randomized controlled trial. *Trials*, 22(1), 747. <https://doi.org/10.1186/s13063-021-05689-5>

flexion du tronc ainsi que l'extension du coude étaient évaluées à l'aide d'un dispositif de capture de mouvement 3D (Kinect V2, Microsoft, USA). De plus, la performance pour la tâche de suivi de trajectoire circulaire était évaluée à l'aide d'un indice de performance effectif (IPE), basé sur la précision (biais) et la vitesse (temps par tour) lors de la réalisation de la tâche (Accot & Zhai, 1999 ; MacKenzie, 1992). Pendant ce temps, l'activité cérébrale de la région SM1 des deux hémisphères était enregistrée à l'aide de 8 électrodes EEG (Starstim8, Neuroelectronics, Barcelona, Spain), et de 8 optodes fNIRS (Octamon+, Artinis Medical Systems, Netherlands), positionnées sur les aires SM1. Pour l'EEG, la variable d'intérêt principale était la perturbation de la puissance spectrale associée au mouvement. Aussi appelée désynchronisation liée à l'évènement (ERD), l'ERD représente une diminution de la puissance d'un rythme. Plus spécifiquement, les ERD des rythmes Alpha (8-13 Hz) et Beta (13-29 Hz) ont été analysés. D'autre part, nous avons quantifié avec la fNIRS, l'amplitude de la réponse hémodynamique via le pic de variation de concentration en oxyhémoglobine (ΔHbO_2).

Etude 1 : Activité cérébrale et cinématique liées à la tâche dans le cadre d'un vieillissement en bonne santé²

Dans cette étude, nous avons cherché à évaluer l'effet du vieillissement en bonne santé sur les schémas d'activation bilatéraux de SM1 lors de mouvements fonctionnels proximaux du MS. À cette fin, nous avons recueilli l'activité cérébrale au cours des deux tâches présentées précédemment. Nous avons inclus dans cette première étude expérimentale deux groupes de personnes en bonne santé : un groupe jeune ($n = 21$; âge moyen = $25,1 \pm 4,7$ ans) et un groupe de sujets âgés sains ($n = 21$; âge moyen = $73,1 \pm 6,7$ ans).

Les résultats de cette première étude expérimentale ont montré que pour la tâche d'atteinte, les stratégies de mouvement entre le groupe jeune et le groupe âgés étaient identiques. Cette absence de différence liée à l'âge a été retrouvée au niveau cérébral avec une absence de réorganisation des régions SM1. Concernant la tâche de suivi de trajectoire circulaire, nous avons retrouvé une diminution des performances pour les sujets âgés, diminution traduite par une réduction de la vitesse de mouvement. Au niveau cérébral, nous avons observé une désynchronisation en EEG au niveau du cortex ipsilatéral plus élevée pour les participants âgés.

Cette étude a permis d'identifier des modifications associées à l'âge à la fois dans la cinématique du mouvement, mais aussi au niveau cérébral dans les patterns de réponse au niveau des deux hémisphères SM1. Le modèle bilatéral d'activation du réseau des régions SM1 observé dans le groupe jeune n'a pas été affecté par le vieillissement pour la tâche d'atteinte. Pour la tâche circulaire avec une contrainte de vitesse/précision, bien que l'activité cérébrale du groupe des personnes âgées en bonne santé se situe à des niveaux similaires à ceux de leurs homologues plus jeunes, la performance globale est plus faible, suggérant une efficacité neuronale réduite.

² Muller, C. O., Perrey, S., Bakhti, K., Muthalib, M., Dray, G., Xu, B., Mottet, D., & Laffont, I. (2023). Aging effects on electrical and hemodynamic responses in the sensorimotor network during unilateral proximal upper limb functional tasks. *Behavioural Brain Research*, 114322. <https://doi.org/10.1016/j.bbr.2023.114322>

Etude 2 : Activité cérébrale et cinématique liées à la tâche dans le cadre de l'AVC³

L'objectif de cette seconde étude était d'explorer l'activité cérébrale associée au mouvement du MS dans la population post-AVC, en examinant comment la pathologie affecte l'activité cérébrale hémodynamique et électrique, et en relation avec la cinématique du mouvement. Pour ce faire, nous avons effectué une comparaison entre les adultes âgés en bonne santé de notre première étude et des adultes victimes d'un AVC afin de déterminer si ces marqueurs cérébraux et de mouvement dans nos tâches fonctionnelles étaient affectés par l'AVC. Le deuxième objectif de cette étude était d'explorer le lien avec la fonction motrice telle qu'elle est évaluée par les scores cliniques. À cette fin, nous avons inclus dans cette étude expérimentale deux groupes : un groupe de personnes âgées en bonne santé (n = 21 ; âge moyen = 73,1 ± 6,7 ans) et un groupe de personnes ayant subi un AVC (n = 21 ; âge moyen = 64,4 ± 10,2 ans).

Concernant les stratégies de mouvement, nous avons observé que les patients victimes d'un AVC étaient plus lents et ce, d'autant plus avec leur bras parétique. De plus, ils utilisaient davantage de compensations et donc présentaient une utilisation moins active de l'articulation coude-épaule, en particulier avec le bras parétique. Au niveau cérébral, nous avons observé une augmentation globale de l'activité cérébrale (fNIRS) et une désynchronisation plus faible (EEG) dans la tâche d'atteinte avec le bras parétique. Cette augmentation de l'activité cérébrale était associée à un plus grand déficit moteur et à une utilisation accrue du tronc dans les tâches.

En conclusion, cette étude a permis l'identification des compensations et des adaptations au niveau du mouvement et de l'activité cérébrale associées à l'AVC. Ces résultats pourraient suggérer des mécanismes de compensation cérébrale pour contrer les effets de l'AVC sur la performance des mouvements. Les paramètres cinématiques et cérébraux ont montré une bonne corrélation avec les scores cliniques, ouvrant de nombreuses perspectives quant à une application en rééducation.

Discussion générale

Evaluation de l'activité cérébrale et du mouvement

Dans les deux études expérimentales réalisées au cours de cette thèse, nous avons confirmé que les signaux fNIRS et EEG communiquaient des informations complémentaires associées à l'activité fonctionnelle du cerveau pendant les mouvements du MS (Chiarelli et al., 2017 ; Yeung et al., 2022 ; Li et al., 2022). En parallèle, le choix des deux tâches visait à reproduire des mouvements nécessitant l'utilisation de toutes les articulations du MS, qui pourraient être comparés à des mouvements de la vie quotidienne (atteindre des objets, s'habiller, se déplacer avec vitesse et précision). La sélection de deux tâches fonctionnelles, différentes dans leur niveau d'exigence et leurs caractéristiques, a permis de mieux rendre compte des effets du vieillissement en bonne santé (l'utilisation de la tâche circulaire est plus discriminante) et de l'AVC (la tâche d'atteinte fournit déjà des informations liées à la pathologie et la tâche circulaire les complète). En somme, associée à l'évaluation clinique, l'exploitation de la cinématique du mouvement pourrait aider à avoir une meilleure quantification de l'évolution du patient, en

³ Muller C.O., Faity G., Muthalib M., Perrey S., Dray G., Xu B., Froger J., Mottet D., Laffont I., Delorme M. & Bakhti. K. (In preparation) Brain-movement relationship in upper-limb functional tasks for chronic post-stroke patients

allant plus loin dans la compréhension de la façon dont la personne effectue le mouvement. Pour résumer, en utilisant différentes tâches et méthodes de neuro-imagerie portables, nous avons proposé une évaluation complémentaire des effets possibles du vieillissement sain et de l'AVC sur l'activité cérébrale et le mouvement.

Stratégies de mouvement et compensation

Malgré des performances moindres dans la tâche de suivi de trajectoire circulaire, les personnes âgées saines semblaient privilégier des stratégies de mouvement similaires à celles des jeunes adultes. Nous pouvons néanmoins émettre l'hypothèse que cela pourrait être dû au niveau d'activité physique / de forme de notre groupe, influencé par leurs capacités physiques. Chez les patients post-AVC, lors de la réalisation de la tâche de suivi de trajectoire circulaire, en accord avec la littérature nous avons trouvé une nette diminution de la performance lors de l'utilisation du MS parétique et plus spécifiquement de la vitesse (Nakayama et al., 1994). Or, nous savons qu'il y a un ralentissement des activités motrices (bradykinésie) qui se produit typiquement avec l'avancée en âge (Salthouse, 2009) et avec l'AVC (Kemper et al., 2002). Ainsi, lier ces marqueurs de mouvement avec des marqueurs au niveau cérébral a permis d'explorer l'effet du vieillissement ou de l'AVC sur les stratégies de mouvement et l'activité cérébrale associée. En ce sens, il a été démontré dans la littérature qu'une vitesse de mouvement accrue était associée à une activité neuronale plus élevée (Tazoe et al., 2013). Ainsi, pour accroître l'activité cérébrale, il pourrait être intéressant d'augmenter la vitesse liée à la tâche. De plus, dans les études sur les AVC, il a été démontré que l'entraînement pour des mouvements à grande vitesse pouvait augmenter l'intensité de l'entraînement spécifique à la tâche (Dejong et al., 2012). Enfin, si l'on s'intéresse aux compensations présentes chez les patients, nous avons pu montrer la compensation du tronc pour les deux tâches du MS. Cette évaluation de la compensation a déjà été présentée dans la littérature (Bakhti et al., 2017). Cependant, nous fournissons ici de nouvelles informations sur l'utilisation de la compensation du tronc en condition spontanée au cours d'une tâche plus difficile (i.e., la tâche de suivi de trajectoire circulaire) par rapport à un mouvement sain.

Compensation cérébrale, vieillissement et AVC

Conformément aux hypothèses de compensation, nos résultats suggèrent que les personnes âgées et les victimes d'AVC recrutent un réseau similaire à celui des adultes en bonne santé, mais l'utilisent de manière inefficace dans la tâche de suivi de trajectoire circulaire. En revanche, dans la tâche d'atteinte, les adultes âgés en bonne santé compensent le déclin neuronal lié à l'âge par une réorganisation plastique des réseaux neuronaux et présentant une activation cérébrale similaire. En examinant nos résultats et la littérature, nous avons mis en évidence la réorganisation cérébrale liée à l'avancée en âge et l'AVC qui semble être associée à la compensation et à la modification de la spécialisation des hémisphères cérébraux (i.e., la perte de la différenciation dans les deux types de vieillissement, sain - Li & Lindenberger 1999 ; et pathologique dans le cas de l'AVC- Schaefer et al., 2007), et à la modification du fonctionnement de l'hémisphère controlésionnel au mouvement. On peut également s'interroger sur la localisation de l'activité cérébrale et sur une éventuelle réorganisation cérébrale en dehors de celle du SM1. En effet, la morphologie des neurones du PFC (cortex préfrontal) est plus

sensible aux changements liés à l'âge, dans la mesure où ces cellules présentent une diminution de la ramification dendritique chez les rats et les humains (Burke & Barnes, 2006). Dans le présent travail, nous n'avons enregistré que l'activité de SM1, de sorte que certaines réorganisations n'ont peut-être pas été évaluées. Ceci est particulièrement vrai pour la tâche circulaire qui induit un feedback visuomoteur et donc, probablement, une activation du PFC (Sakurada et al., 2019). Néanmoins, en ce qui concerne la tâche d'atteinte, la réorganisation liée à l'âge du cerveau a montré une hyperactivité chez les patients ayant subi un AVC, ce qui confirme le fait que quelques activations passaient encore par les cortex moteurs.

Vieillir mieux et mieux récupérer après un AVC

Dans le cadre du vieillissement sain, l'objectif est de maintenir un niveau élevé de fonction. Ce type de vieillissement dît robuste, est caractérisé par le maintien des capacités fonctionnelles où leur altération demeure modérée. Dans ce contexte, l'approche fonctionnelle est pertinente pour distinguer les différentes modalités de l'avancée en âge. Elle intègre entre autres la notion de réversibilité ou de plasticité, qui rend compte de la possibilité de changer de trajectoire sous l'effet d'actions adaptées. Nous pouvons imaginer que l'évaluation fonctionnelle de l'activité cérébrale liée à la tâche proposée pourrait être utilisée pour suivre l'évolution du vieillissement en bonne santé, par le biais du mouvement et de la réorganisation cérébrale. Avec cette idée, nous pourrions éventuellement guider la gestion du vieillissement, en orientant les personnes âgées vers une activité physique adaptée par exemple.

Si l'on s'intéresse à l'orientation de la prise en charge des patients pos-AVC à l'aide de la méthode utilisée pour cette thèse, la difficulté ici est de différencier réellement quelle réduction de fonction provient du vieillissement physiologique, et laquelle résulte des déficiences pathologiques post-AVC. Ce point souligne l'importance de différencier la gestion des soins selon si l'on fait face à un jeune patient post-AVC ou à un patient plus âgé. La stimulation de la plasticité cérébrale semble être la solution à l'altération des fonctions du MS que l'on soit dans un contexte pathologique ou non. Elle pourrait être induite grâce à une réponse dépendante de l'expérience en proposant aux sujets des programmes d'activités physiques, de réalité virtuelle ou de stimulation cérébrale non invasive, ou les deux combinés.

Conclusion

Dans le cadre de ce projet de thèse, nous avons observé une modification des mouvements lors du vieillissement en bonne santé (i.e., une réduction des performances) et lors d'un accident vasculaire cérébral (i.e., un recours accru aux compensations du tronc et une réduction de la vitesse de mouvement). En outre, nous avons observé une augmentation de l'activité ipsilatérale chez les personnes âgées pour atteindre un niveau de performance élevé dans la tâche de suivi de trajectoire circulaire. C'est également le cas chez les patients lors de la tâche d'atteinte, et surtout chez les patients présentant une déficience plus importante du MS, qui doivent utiliser davantage de ressources neuronales pour réaliser les mouvements d'atteinte. Ces résultats permettent de mieux comprendre les modifications neurophysiologiques associées au processus de vieillissement et à la parésie du MS après un AVC.

Ce travail de thèse ouvre une fenêtre sur l'utilisation de marqueurs supplémentaires de la récupération du MS au niveau de la cinématique du mouvement (dispositifs de capture du mouvement sans capteur) et de l'activité cérébrale (fNIRS et EEG portables). D'un point de vue clinique, il est possible d'utiliser une telle évaluation fonctionnelle afin d'optimiser la prise en charge des patients. Si l'on considère la rééducation post-AVC, les tâches proposées pourraient être utilisées pour évaluer l'évolution du niveau de récupération de l'individu, en permettant d'observer l'évolution du niveau d'activité cérébrale et des performances pendant les mouvements fonctionnels proximaux du MS. Une perspective majeure de ce travail serait donc d'utiliser ces méthodes dans le cadre de la rééducation afin de mieux décrire les marqueurs concrets de la récupération du MS au fil du temps, et mieux comprendre les effets bénéfiques d'une méthode de rééducation ou d'une autre et ainsi s'orienter le plus possible vers une individualisation de la prise en charge des patients en rééducation.

CONTEXTE : VIEILLISSEMENT

↑ personnes âgées et risque d'AVC ↓ Fonction du membre supérieur (MS)
Objectif = améliorer la fonction du MS pour une meilleure vie au domicile

↑ FONCTION DU MS

Meilleure connaissance de la relation cerveau-mouvement fonctionnel

Méthodes de neuro-imagerie

- ❑ Facile à utiliser et combiner
- ❑ En condition écologique
- + *adaptées : fNIRS et EEG*

Evaluation de la fonction du MS

- ❑ Evaluation objective
- ❑ Evaluation facile et rapide
- + *adaptée : Cinématique*

ACTIVITÉ CÉRÉBRALE DU MOUVEMENT DU MS

Jeunes sains

- ❑ Pour les mouvements unilatéraux, activation controlatérale plus élevée

Âgés sains

- ❑ Augmentation de l'activation de l'hémisphère ipsilatéral pour atteindre des niveaux de performance similaires

Âgés pathologiques (AVC)

- ❑ Différentes implications de l'hémisphère sain en fonction du stade de l'AVC et de la rééducation

Contribution expérimentale de la thèse

Méthode

Stratégie du mouvement proximal unilatéral
 → Tâche d'atteinte
 → Tâche de suivi de trajectoire circulaire
 Enregistrement de SM1
 → EEG
 → fNIRS

Effets du vieillissement sain

Cinématique

- Performances réduites mais dominance manuelle préservée
- Pas de compensations

Cerveau

- Activité ipsilatérale plus élevée pendant la tâche de suivi de trajectoire circulaire
- Tendance à un ERS plus bas

Effets de l'AVC

Cinématique

- Compensations du tronc
- Vitesse réduite

Cerveau

- Augmentation de l'activation en tâche d'atteinte avec le bras parétique

Relations entre...

- Scores cliniques, paramètres cinématiques et cérébraux



Perspectives ?

- ❑ Explorer la cinématique et l'activité cérébrale associée lors de la rééducation post-AVC pour attester des effets des différentes méthodes de rééducation
- ❑ Explorer plus d'aires cérébrales telles que les aires frontales très impliquées lors de tâches impliquant un contrôle visuomoteur
- ❑ Tester une population plus âgée
- ❑ Explorer des tâches plus distales et/ou des doubles tâches

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